Estudio, mediante potenciales evocados, de la interferencia de las dimensiones irrelevantes del estímulo en tareas tipo Simon. Efectos de la edad y del deterioro cognitivo ligero.

Tesis Doctoral

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ABSTRACT

In the present dissertation, several cognitive tasks were designed, specifically stimulus-response compatibility (SRC) tasks, which were implemented in samples of healthy young, middle-aged, elderly participants and participants diagnosed of Mild Cognitive Impairment (MCI). The research aimed to obtain electrophysiological correlates of cognitive processes and changes in these electrophysiological correlates related with ageing and the MCI state.

The Simon tasks are a type of SRC task in which participants respond to one feature of a lateralized stimulus (e.g., the stimulus colour) by pressing one of two buttons disposed in the same spatial arrangement that the presentation of the stimuli. The Reaction Time (RT) is slower when the stimulus position is spatially contralateral (and thus, incompatible) to the side of the required response. That slowing in RT is known as the Simon effect. Event-related brain potential (ERP) studies established the locus of the Simon effect in the response selection stage using the lateralized readiness potential (LRP), an ERP component that allows distinguishing between interference in perceptual and motor stages of processing.

The ERP studies with Simon-type tasks usually presented the stimuli in a vertical arrangement to avoid the overlap of the LRP with the N2 posterior contralateral (N2pc) and the N2 central contralateral (N2cc). However, considering that N2pc is a correlate of visuospatial processing of lateralized stimuli and N2cc is involved in preventing the bias of responding towards the side where the attention is directed, N2pc and N2cc might play an important role in the Simon effect. Nonetheless, previous studies did not research on the N2cc modulation between experimental conditions and those studying the N2pc modulations are scarce and showed contradictory results.

In the present research, three different SRC tasks (which required response to coloured stimuli) were designed. These tasks were implemented in a sample of young participants. The tasks differed in the source of the irrelevant dimension: stimulus position (SRC task based on the position –left or right-: SRC-p), arrow direction (SRC task based on the direction -left or right-: SRC-d), and both (SRC task based on the position and direction of an arrow: SRC-pd). The SRC-pd was also implemented in samples of healthy middle-aged and elderly participants, as well as in MCI participants.

Regarding the basic electrophysiological research, a first study (Study 1) was conducted with the SRC-p task. In this study, a central stimulus was used to remove the common motor activity between this and the lateralized conditions. Therefore, it was possible studying N2pc and N2cc modulations without contamination by motor activity (LRP). The eLORETA analyses showed greater premotor activity in both lateralized conditions in comparison to the neutral condition. This activity was related with the N2cc component. Also, N2cc was larger in the incompatible than in the compatible condition, which was consistent with greater premotor activity for monitoring the selection of the correct response in the incompatible condition. N2pc was not modulated by the stimulus position suggesting that processes of visuospatial attention were not an interference locus, as demonstrated by previous studies. However, N2pc had been modulated by the Simon effect in a study where the participants responded to the direction of a lateralized arrow (Valle-Inclán, 1996, exp 2). Thus, interference from the stimulus position was accompanied by a conflict of spatial information (i.e., the arrow direction pointed to the opposite side regarding the hemifield where it was located). Consequently, effects could be attributed to position interference but also to perceptual conflict.

In a second study (Study 2), the SRC-pd task was used for dissociating motor interference and perceptual conflict. As result of combining the two irrelevant dimensions (position and direction), the task resulted in the following conditions: Compatible Direction-Compatible Position (CDCP); Incompatible Direction-Compatible Position (IDCP); Compatible Direction-Incompatible Position (CDIP); and Incompatible Direction-Incompatible Position (IDIP). In IDCP and CDIP, the two irrelevant dimensions conveyed contradictory spatial information while in CDCP and IDIP both irrelevant dimensions carried congruent spatial information (i.e. the direction indicated was compatible with the stimulus position). The N2pc amplitude was smaller in IDCP and CDIP than in CDCP and IDIP, suggesting that N2pc was modulated by the perceptual conflict and not by motor interferences.

A third study (Study 3) compared the interference from the stimulus position (in the SRC-p task) and arrow direction (in the SRC-d task) since behavioural evidence showed that the stimulus position was processed faster than the arrow direction whereas that ERP studies suggested similar interference loci. The results of the Study 3 replicated the existence of the previously mentioned behavioural differences between the SRC-p and the SRC-d task. The electrophysiological data showed a similar locus of

interference in motor processes for both S-R incompatibilities; however, unlike of previous ERP studies, P3b (link between stimulus evaluation processes and response onset) was only modulated by the stimulus position. It was discussed that P3b modulations by incompatibility from the direction observed in previous studies were not unequivocally related with interference from the direction. In those studies a low proportion of incompatible trials, relative to neutral and/or compatible trials, were presented. Therefore, in it was not possible to attribute P3b modulations to the effect of the arrow direction or to the low proportion of presented incompatible trials (i.e., to the oddball design).

A subsequent study (Study 4) focused on age-related changes in correlates of visuospatial and motor processes in samples of young, middle-aged and elderly participants. The motor execution stage (studied through response-locked LRP –LRP-r-) was progressively slowed with age whereas visuospatial processes (N2pc latency) were slower in middle-aged and elderly than in young participants but differences were not present between the middle-aged and the elderly groups. It supported a specific pattern of age-related cognitive slowing on each particular process. Also, the distributional analyses of the RT showed that the interference from the direction affected to faster responses in young participants, to slower responses in middle-aged participants, and did not affect in elderly participants. These results suggested that the processing of the direction of the arrow was disproportionately delayed in comparison to the processing of the arrow colour (which conditioned the time of emitting the response). Results from N2pc amplitude showed that the conflict of spatial information conveyed by the two irrelevant dimensions only affected to young participants, which was consistent with no processing of the arrow direction in middle-aged and elderly groups.

Another study (Study 5) focused on modulations in ERP correlates of visuospatial (N2pc) and motor processes (LRP-r) in samples of healthy participants and participants diagnosed of amnestic mild cognitive impairment (aMCI). Although behavioural performance was similar between healthy adults and aMCI participants, N2pc was smaller in aMCI than in the control group, suggesting a reduction in the allocation of visuospatial attention to the target stimulus. Furthermore, LRP-r amplitude was smaller in aMCI than in the control group, which was consistent with recent studies that suggested a deficit in motor cortex in MCI participants. Interestingly, the LRP-r amplitude proved to be a good marker of aMCI (Area under curve: 0.86; sensitivity: 0.85; specificity: 0.92).

In summary, the present research studied the modulation of ERP correlates of visuospatial, motor, and cognitive control processes in SRC tasks. In addition, it compared the interference loci between spatial interferences induced by stimulus position and by a symbolic signal (i.e., the direction pointed by a central arrow). Also, in the frame of the neuropsychological ageing, contributions were made to the cognitive slowing theory, and to the obtaining of aMCI biomarkers.

RESUMEN

En el presente trabajo de investigación se diseñaron varias tareas cognitivas, concretamente tareas de compatibilidad estímulo-respuesta (CER). Estas tareas cognitivas fueron aplicadas a muestras de participantes jóvenes, de mediana edad y mayores sanos, así como en adultos (de mediana edad y mayores) diagnosticados de deterioro cognitivo ligero (DCL). Esta investigación pretendía estudiar correlatos electrofisiológicos de procesos cognitivos y cambios, en dichos correlatos, relacionados con el envejecimiento sano y el DCL.

Las tareas de CER son tareas cognitivas que se caracterizan por la existencia de solapamientos entre una dimensión del estímulo, que es relevante para la tarea (y en base a la cual el participante debe emitir una respuesta), y la dimensión de respuesta u otras dimensiones del estímulo, que son irrelevantes para la ejecución de la tarea. La incompatibilidad entre la dimensión relevante del estímulo y la dimensión de respuesta u otra dimensión irrelevante del estímulo produce un efecto de interferencia. Este efecto de interferencia se manifiesta en un enlentecimiento del tiempo de reacción (TR). El modelo del solapamiento dimensional (Zhang, Zhang, & Kornblum, 1999) incluye una taxonomía en la que se distinguen 8 tipos de tareas de CER en función de los solapamientos existentes entre las dimensiones relevante e irrelevante del estímulo y entre estas dos dimensiones del estímulo con respecto a la respuesta.

Las tareas Simon son un tipo de tareas de CER tipo 3, en las cuales una dimensión del estímulo, que es irrelevante para la tarea, se solapa con la respuesta. En concreto, los participantes tienen que responder a una característica de un estímulo (por ejemplo, el color), que se encuentra espacialmente lateralizado, presionando uno de dos botones de respuesta que están en la misma disposición espacial que los estímulos presentados. En estas tareas, el TR es más lento cuando la posición del estímulo es espacialmente contralateral (y por tanto incompatible) con respecto a la ubicación de la tecla de respuesta. Este enlentecimiento en el TR es conocido como el efecto Simon. Mediante la técnica de potenciales evocados (PE), el locus de interferencia del efecto Simon se estableció en la selección de la respuesta. Este hallazgo fue obtenido mediante el uso del potencial de preparación lateralizado (PPL), un componente de los PE componente que permite distinguir entre interferencias que ocurren en estadios perceptuales e interferencias que tienen lugar en estadios motores del procesamiento.

Los estudios de PE con tareas tipo Simon normalmente presentaron los estímulos en disposición vertical, con el fin de evitar el solapamiento del PPL con los componentes N2 posterior contralateral (N2pc) y N2 central contralateral (N2cc). De este modo, la disposición vertical de los estímulos es ideal para realizar inferencias sobre el locus del efecto Simon a partir de modulaciones del PPL. Sin embargo, considerando que N2pc es un correlato del procesamiento espacial de estímulos lateralizados y que N2cc se relacionó con actividad que impide la tendencia automática a responder en función de la localización a la que se dirigen los recursos atencionales, N2pc y N2cc podrían jugar un importante papel en los procesos relacionados con el efecto Simon. Con todo, la inmensa mayoría de las investigaciones se centraron en el estudio del PPL y todavía permanece sin estudiar la posible modulación del componente N2cc por el efecto Simon. Además, los estudios sobre cómo el efecto Simon modula N2pc son escasos y mostraron resultados contradictorios.

En la presente investigación se diseñaron tres tareas de CER, en las cuales se requería responder al color de los estímulos presentados. Estas tres tareas fueron implementadas en una muestra de participantes jóvenes. Las tareas se diferenciaban en la fuente de la información irrelevante: la posición del estímulo (tarea de CER basada en la posición, o CER-p), la dirección de la flecha (tarea de CER basada en la dirección apuntada por la flecha, o CER-d) y la combinación de ambas, es decir, la posición del estímulo y la dirección apuntada por la flecha (tarea de CER basada en la posición del estímulo y en la dirección de la flecha, o CER-pd). La tarea de CER-pd fue además implementada en muestras de adultos sanos de mediana edad y ancianos, así como en participantes diagnosticados de DCL.

Con respecto a la investigación básica sobre correlatos electrofisiológicos de procesos cognitivos que tienen lugar durante la ejecución de una tarea Simon, se llevó a cabo una primera investigación con la tarea CER-p (Estudio 1, Cespón, Galdo-Álvarez & Díaz, 2012) que se centró fundamentalmente sobre el estudio de N2cc y N2pc. En este estudio se utilizó un estímulo central para eliminar la actividad motora común entre éste estímulo y los estímulos lateralizados (es decir, los estímulos compatibles en posición –CP- e incompatibles en posición –IP-). De esta forma, sería posible estudiar las modulaciones de N2pc y N2cc sin contaminación en ambos componentes por actividad motora (PPL).

Los análisis realizados mediante eLORETA mostraron mayor actividad premotora, entre 150 y 200 ms, en las condiciones donde los estímulos estaban

espacialmente lateralizados (CP e IP) que en la condición neutral (NP), en la cual el estímulo se presentaba en una posición central. Esta actividad fue relacionada con el componente N2cc. Además, en los trazados en los cuales se sustrajo la actividad motora se obtuvo una mayor amplitud de N2cc en la condición incompatible que en la compatible, lo cual resultó consistente con una mayor actividad premotora para monitorizar la selección de la respuesta correcta en la condición incompatible. Por lo tanto, N2cc es el correlato de un importante mecanismo de control cognitivo que tiene lugar en tareas Simon. Por otra parte, N2pc no fue modulada por la posición del estímulo. Este resultado sugirió que los procesos de atención visoespacial no constituían un locus de interferencia en el efecto Simon, tal y como previos estudios habían demostrado. Además, este resultado apoya la disociación funcional entre ambos componentes, teniendo en cuenta que el efecto Simon moduló N2cc (considerado un correlato de mecanismos de control cognitivo para impedir la emisión de una respuesta automática con la mano ipsilateral con respecto a la dirección del cambio atencional) pero no N2pc (considerado un correlato de atención visoespacial al estímulo target).

Aunque N2pc no fue modulada por el efecto Simon en la tarea CER-p, lo cual fue consistente con algunos estudios previos (Praamstra & Oostenveld, 2003; Van der Lubbe & Verleger, 2001), N2pc había sido modulada por el efecto Simon en Valle-Inclán (1996, exp 2). Esta aparente inconsistencia podría explicarse considerando que, en el estudio de Valle-Inclán (1996, exp 2), los participantes respondían a la dirección de una flecha que se encontraba espacialmente lateralizada. Por lo tanto, en esta tarea, la interferencia de la posición del estímulo (interferencia estímulo-respuesta, E-R) era acompañada por un conflicto de información espacial. Es decir, la flecha apuntaba hacia el lado opuesto con respecto al hemicampo donde estaba situada (incongruencia estímulo-estímulo, E-E). Consecuentemente, los efectos podían ser atribuidos a la interferencia de la posición (esto es, al efecto Simon) pero además a un conflicto perceptivo producido por la información espacial incongruente portada por las dos dimensiones irrelevantes (la dirección apuntada por la flecha y su posición). Desafortunadamente, las condiciones experimentales de la tarea empleada por Valle-Inclán (1996, exp 2) no permitían disociar la interferencia producida por la incompatibilidad de la posición y el conflicto de información espacial puesto que el conflicto E-E covariaba con la interferencia E-R; es decir, la incompatibilidad de la posición era acompañada de incongruencia espacial entre la dirección de la flecha y la

posición del estímulo mientras que cuando la posición era compatible con la respuesta la flecha apuntaba hacia el mismo lado con respecto a donde estaba ubicada.

En un segundo estudio (Estudio 2, Cespón, Galdo-Álvarez, & Díaz, 2013), la tarea CER-pd fue utilizada para disociar la interferencia motora y el conflicto perceptivo. Como resultado de combinar las dos dimensiones irrelevantes (posición y dirección), la tarea daba lugar a las siguientes condiciones experimentales: Compatible Dirección-Compatible Posición (CDCP); Incompatible Dirección-Compatible Posición (IDCP); Compatible Dirección-Incompatible Posición (CDIP); and Incompatible Dirección-Incompatible Posición (IDIP). En las condiciones IDCP y CDIP, ambas dimensiones irrelevantes portaban información espacial contradictoria (la flecha apuntaba hacia el lado contrario con respecto a donde estaba ubicada) mientras que en CDCP e IDIP las dos dimensiones irrelevantes portaban información espacial congruente (esto es, la dirección indicada por la flecha era compatible con la posición de la misma). La amplitud de N2pc fue menor en las condiciones IDCP y CDIP (condiciones en las cuales la flecha apuntaba hacia el lado contrario con respecto a donde estaba ubicada) que en las condiciones CDCP e IDIP (condiciones en las cuales la dirección apuntada por la flecha y la posición de la misma eran espacialmente compatibles).

En base a la evidencia comentada en el párrafo anterior puede inferirse que en el estudio de Valle-Inclán (1996, exp 2) la amplitud de N2pc fue modulada por el conflicto de información espacial (incongruencia E-E) y no por la interferencia E-R. Sin embargo, en el estudio de Valle-Inclán (1996, exp 2) el conflicto de información espacial estuvo relacionado con un aumento en la amplitud de N2pc. Por el contrario, en el Estudio 2 de la presente investigación (Cespón et al., 2013) la amplitud de N2pc fue menor cuando ambas dimensiones irrelevantes portaban información espacial contradictoria. Esta aparente inconsistencia puede ser el resultado de diferencias entre los diseños experimentales de ambos estudios. Concretamente, en el presente estudio los estímulos target y no target estaban separados por 7.5º de ángulo visual por lo que es muy probable que, bajo estas condiciones la N2pc refleje básicamente procesos relacionados con el procesamiento del estímulo target. Sin embargo, en el estudio de Valle-Inclán (1996, exp 2) los estímulos target y no target estaban separados por 1º de ángulo visual por lo que es muy probable que en ese estudio la amplitud de N2pc estuviese reflejando procesos relacionados con el procesamiento del estímulo target pero también con la supresión del estímulo no target.

Un tercer estudio (Estudio 3, Cespón, Galdo-Álvarez, & Díaz, en revisión editorial, a) comparó la interferencia de la posición del estímulo (tarea CER-p) con la interferencia de la dirección de la flecha (tarea CER-d) puesto que la evidencia conductual, obtenida por medio del análisis de distribución de tiempos de reacción, mostraba que la posición del estímulo era procesada más rápidamente que la dirección de la flecha. Sin embargo, estudios de PE sugerían que el locus de interferencia era idéntico para ambas incompatibilidades E-R.

Los resultados del Estudio 3 replicaron la existencia de las diferencias conductuales previamente mencionadas entre la incompatibilidad de la posición (estudiada mediante la tarea CER-p) y la incompatibilidad de la dirección de la flecha (estudiada mediante la tarea CER-d). Dichas diferencias podrían resumirse en los siguientes puntos: 1) la interferencia de la posición era mayor que la interferencia de la dirección; 2) la posición del estímulo interfería desde los TR más rápidos mientras que la interferencia de la dirección de la flecha sólo era significativa en los TR más lentos; 3) la dirección de la flecha, pero no la posición del estímulo, produjo un efecto de facilitación en la condición en la que era compatible con la respuesta al color.

Los resultados electrofisiológicos revelaron un locus de interferencia, para ambas tareas, en procesos motores. Este locus de interferencia fue evidenciado mediante la utilización del potencial de preparación lateralizado en relación con la respuesta (PPL-r). Concretamente, en la condición incompatible de las dos tareas, se observaba un retraso en la latencia de inicio del PPL-r, el cual era precedido por una transitoria preparación de la respuesta incorrecta. Por lo tanto, ambas tareas compartían un locus de interferencia en procesos relacionados con la respuesta.

Por otro lado, y a diferencia de lo encontrado en estudios previos, P3b (nexo entre procesos de evaluación del estímulo y selección de la respuesta) sólo fue modulado por la posición del estímulo (latencia más lenta y amplitud menor cuando la posición del estímulo era incompatible con la respuesta). Los resultados mostraron que, incluso en TR lentos donde no existían diferencias entre la magnitud de la interferencia de la dirección y de la posición, P3b sólo fue modulado por la posición del estímulo. De este modo, la ausencia de modulación de estos procesos por la interferencia de la dirección no fue debida a diferencias en tamaño del efecto entre ambos tipos de interferencia. La discusión del Estudio 3 se centra en el hecho de que las modulaciones de P3b por la incompatibilidad de la dirección observadas en estudios previos podrían estar relacionadas con una baja proporción de ensayos incompatibles presentados en

esos estudios. Es decir, el bajo número de ensayos incompatibles, en comparación con el número de compatibles y / o neutrales, daba lugar a un paradigma tipo oddball, el cual demostró modular los parámetros de P3b. Así, en esos estudios previos no se podía establecer, de forma inequívoca, si el componente P3b había sido modulado por el efecto de la dirección o por la baja proporción de ensayos incompatibles.

En resumen, el Estudio 3, además de evidenciar la existencia de diferencias conductuales y electrofisiológicas entre la interferencia de la posición y la interferencia de la dirección de una flecha, puso de manifiesto la importancia del control de ciertas variables que pueden afectar a la modulación de los componentes de los PE y por lo tanto a la interpretación de los resultados.

Se llevó a cabo un cuarto estudio (Estudio 4, Cespón, Galdo-Álvarez, & Díaz, en prensa) focalizado en los cambios relacionados con la edad en correlatos de procesos visoespaciales (N2 posterior contralateral –N2pc-) y motores (potencial de preparación lateralizado –PPL-) en muestras de participantes jóvenes (18-27 años), de mediana edad (50-64 años) y mayores (65-84 años).

Los procesos de ejecución motora (estudiados mediante el PPL-r) mostraron un progresivo enlentecimiento con la edad mientras que los procesos visoespaciales (latencia de N2pc) fueron más lentos en los participantes de mediana edad y ancianos que en los jóvenes, sin encontrar diferencias entre los grupos de mediana edad y ancianos. Estos resultados apoyaron la existencia de un patrón de enlentecimiento relacionado con la edad que fue específico para cada proceso cognitivo. Además, el análisis de distribución de los TR mostró que la interferencia de la dirección afectaba a respuestas rápidas en participantes jóvenes y a respuestas lentas en participantes de mediana edad mientras que dicha interferencia no era manifestada en el grupo de mayores. Estos resultados sugirieron que el procesamiento de la dirección de la flecha en participantes mayores estaba desproporcionadamente enlentecido en comparación con el procesamiento del color, el cual condicionaba el momento en el que se emitía la respuesta. Los resultados sobre la amplitud de N2pc mostraron que el conflicto de información espacial entre las dos dimensiones irrelevantes sólo afectaba a participantes jóvenes, es decir, N2pc fue menor en IDCP y CDIP que en CDCP e IDIP en el grupo de jóvenes pero en los grupos de mediana edad y de mayores la amplitud de N2pc no fue modulada por las condiciones experimentales. Este resultado indicó ausencia de conflicto E-E en los grupos de mayor edad y fue consistente con la ausencia de procesamiento de la dirección.

En cuanto a la magnitud de la interferencia, no se encontraron diferencias significativas relacionadas con la edad. Este hallazgo fue inconsistente con la teoría del déficit de control inhibitorio relacionado con la edad. Probablemente, el retraso en el procesamiento de la dirección de la flecha contribuyó a atenuar posibles diferencias relacionadas con la edad en las tres condiciones donde estaba presente alguna de las incompatibilidades E-R (IDCP, CDIP e IDIP). Específicamente, si el procesamiento de la dirección apuntada por la flecha es enlentecido, entonces sería esperable que no existiese ningún tipo de interacción entre la posición y la dirección en la condición donde ambas dimensiones irrelevantes eran incompatibles con la respuesta al color (IDIP). Además, el antedicho enlentecimiento en el procesamiento de la dirección en los participantes de mediana edad y mayores daría lugar a que, en las condiciones IDCP y CDIP, el conflicto de información espacial no estuviese presente en estos dos grupos, lo cual elimina una posible fuente de enlentecimiento sobre los TR.

Otro de los estudios (Estudio 5, Cespón, Galdo-Álvarez, & Díaz, en revisión editorial, b) se centró en la investigación sobre posibles biomarcadores del DCL amnésico (DCLa). En este trabajo se estudió la modulación de los correlatos electrofisiológicos de procesos visoespaciales (N2pc) y motores (PPL) en una muestra de participantes de mediana edad y mayores sanos, así como en participantes diagnosticados de DCLa. Considerando que Iachini, Ivarone, Senese, Ruotolo, & Ruggiero (2009) evidenciaron que déficits conductuales en habilidades visoespaciales aparecían tempranamente en la progresión desde el envejecimiento sano hacia la enfermedad de Alzheimer, la obtención de correlatos de procesos visoespaciales podría ser un enfoque adecuado para la obtención de biomarcadores. Por otra parte, algunos estudios recientes, utilizando estimulación magnética transcraneal (por ejemplo Tsutsumi et al., 2012), sugerían alteraciones en la corteza motora en participantes diagnosticados de DCL. Además, como se mencionó anteriormente, los procesos relacionados con la respuesta constituyen una fuente de enlentecimiento relacionado con la edad. Teniendo en cuenta que este enlentecimiento puede verse incrementado en participantes diagnosticados de DCL y las anteriormente mencionadas alteraciones en la corteza motora en participantes diagnosticados de DCL, el PPL se consideró un componente especialmente interesante para la obtención de correlatos y posibles biomarcadores de DCLa.

Los resultados mostraron que la ejecución conductual fue similar en adultos sanos y participantes diagnosticados de DCLa. Es decir, no se observaron diferencias en

enlentecimiento (estudiado mediante el tiempo de reacción y las latencias de los componentes N2pc y PPL-r) ni en la magnitud de la interferencia. Sin embargo, la amplitud de N2pc fue menor en DCLa que en el grupo control, sugiriendo una reducción, en el grupo DCLa, de los recursos atencionales dedicados al procesamiento del estímulo target. Además, la amplitud del PPL-r fue menor en DCLa que en el grupo control, lo cual fue consistente con estudios recientes que sugirieron un déficit en la corteza motora en pacientes diagnosticados de DCL.

Un hallazgo destacable es que la amplitud del PPL-r mostró ser un buen biomarcador de DCLa (área bajo la curva: 0.86, sensibilidad: 0.85; especificidad: 0.92). Sin embargo, la amplitud de N2pc no alcanzó unos valores de sensibilidad y especificidad suficientes para ser considerado un buen biomarcador de DCLa. No obstante, es importante tener en cuenta que las amplitudes de PPL-r y N2pc constituyen correlatos de DCLa y que ambos correlatos sugieren déficits electrofisiológicos que están presentes en ausencia de evidencia conductual (puesto que no hubo ninguna diferencia en las medidas conductuales entre los dos grupos de participantes). Este hecho es consistente con que el deterioro fisiológico es anterior a la manifestación de alteraciones conductuales y apoya la utilidad de los potenciales evocados para la obtención de biomarcadores tempranos de DCL.

En resumen, en la presente investigación se estudió la modulación de correlatos electrofisiológicos de procesos visoespaciales, motores y de control cognitivo en tareas de CER. Además, se compararon los locus de interferencia producidos por información espacial irrelevante en función de si ésta era proporcionada por la posición del estímulo o por una señal simbólica (la dirección apuntada por una flecha central). Además, en el marco del envejecimiento neuropsicológico, el presente trabajo realizó contribuciones principalmente a la teoría del enlentecimiento cognitivo y a la obtención de biomarcadores del DCLa.

1. Introduction

The present research was conducted using samples of human participants that performed different cognitive tasks whereas the electroencephalographic (EEG) activity was recorded. The aims were: 1) to study electrophysiological correlates of cognitive functions, mainly related with visuospatial attention and motor processes, in samples of healthy young participants; 2) to test the age-related changes in the electrophysiological correlates of the above cognitive functions, which required also the recruitment of samples of middle-aged and elderly participants; 3) to evaluate whether these electrophysiological correlates were able to distinguish between healthy adult participants and participants with amnestic Mild Cognitive Impairment (aMCI). Thus, a sample of aMCI participants was also recruited. The search for biomarkers of MCI in its early stages through the EEG technique is especially interesting since EEG is a low cost, non-invasive and widely diffused procedure (Rossini et al., 2006).

1.1 The stimulus-response compatibility tasks

The stimulus-response compatibility tasks (SRC) are a type of tasks where the participants are instructed to emit a response based on a feature of the stimulus (i.e., the relevant dimension of the stimulus). This relevant dimension may be overlapped with other dimensions of the stimulus and / or of the response, which are irrelevant for performing the task. However, when the irrelevant dimension activates a response that is incompatible with the response based on the instructions, an effect of interference is produced, which is manifested by a slower reaction time (RT) in that condition. Zhang, Zhang, and Kornblum (1999) distinguished eight types of SRC-tasks according to the number and characteristics of overlaps between the relevant and the irrelevant stimulus dimension or between the relevant stimulus dimension and the response. In addition,

these authors developed a model, known as the dimensional overlap model (Kornblum, Hasbroucq, & Osman, 1990; Kornblum & Lee, 1995; Zhang et al., 1999), which grouped under a same theoretical approach the eight types of SRC tasks, which usually had been separately studied (e.g. Flanker task, Simon task, or Stroop task).

In the present research, the specific election of the tasks, for implementing in the samples of participants, obviously depended on the processes to study. Specifically, we were interested in investigating electrophysiological changes related with the ageing and the amnestic mild cognitive impairment (aMCI). For this purpose, it was pertinent to focus on those electrophysiological correlates that probably would show differences related with age and aMCI.

On the one hand, the present research studied visuospatial processes, which on the basis of behavioural data had been reported to decline with ageing and especially at early stages in the progression from normal ageing to Alzheimer`s disease (Iachini, Ivarone, Senese, Ruotolo, & Ruggiero, 2009). This fact led to Iachini et al (2009) to suggest that the search of biological correlates of visuospatial processes was an interesting approach for obtaining biomarkers at very early phases of the AD. On the other hand, event-related potential (ERP) studies partially supported the cognitive slowing theory with ageing (Salthouse, 2009) and suggested that the main source of that cognitive slowing was the prolongation of the motor execution stage (Kolev, Falkenstein, & Yordanova, 2006). Interestingly, behavioural investigations suggested an additional slowing in RT at very early stages in the progression from normal ageing to AD as well as increased motor interference (Castel, Balota, Hutchison, Logan, Yap, 2007). Therefore, it seems pertinent also focusing on response-related processes in the study of differences related to the age and the MCI state.

The SRC tasks used for studying the cognitive processes of interest (basically, visuospatial attention, motor execution and inhibition processes) were Simon-type tasks (for a review see Lu & Proctor, 1995) (the tasks used in the present study were graphically represented in Figure 1). The Simon tasks are a type-3 SRC task in which an irrelevant dimension of the stimulus overlaps with the response. Specifically, in Simon tasks the participants respond to a feature of a stimulus (e.g., the stimulus colour) that appears spatially lateralized (i.e. the stimulus is localized on the right or on the left regarding the centre of the screen) by pressing one of two response buttons (disposed in the same spatial arrangement that the presentation of the stimuli). The stimulus position is irrelevant for the performance. However, in those cases in which the required response is on the opposite side to the stimulus (incompatible condition), an interference effect known as the Simon effect is produced. The Simon effect is revealed by longer reaction times (RT) in the incompatible condition in comparison to the compatible condition, in which the stimulus position and the response side are spatially compatible.

In the present research, the Simon-type tasks were considered appropriate for investigating the previously mentioned processes. Specifically, in the Simon tasks the stimuli are spatially lateralized whereby visuospatial attention to lateralized stimuli can be studied. Regarding these processes, the N2 posterior-contralateral (N2pc) is an ERP component that would allow studying the visuospatial processing of lateralized stimuli (Luck and Hillyard, 1994; Woodman and Luck, 1999). Also, as the participants had to response to the colour of the stimulus (preventing also the described automatic tendency of responding toward the side compatible with stimulus position) the motor and inhibitory processes can be investigated, in this case, through the lateralized readiness potential (LRP), a ERP correlate of motor activity related with the limb involved in selecting and executing a response (see Gratton Coles, Sirevaag, Eriksen, and Donchin,

1988). Consequently, the present research focused on ERP correlates of visuospatial, motor and inhibitory control processes for investigating the changes related with ageing and the aMCI state in samples of healthy young, middle-aged and elderly participants as well as in participants diagnosed of aMCI.

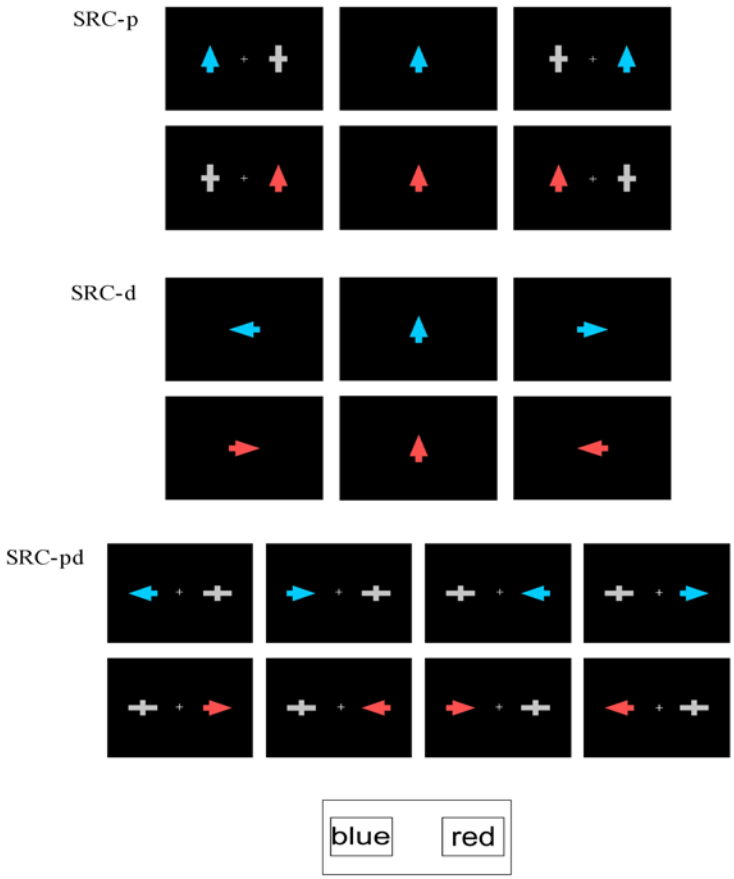

Figure 1. Schematic representation of the stimulus-response compatibility (SRC) tasks. In the three tasks the participants responded to the arrow colour by pressing one of two buttons disposed in horizontal arrangement. The tasks differed in the irrelevant dimension: the stimulus position (SRC-p task, top panel), the direction pointed by the arrow (SRC-d task, middle panel), the position and the direction pointed by the arrow (SRC-pd task, bottom panel). For the SRC-p and SRC-d tasks the experimental conditions were (from left to right): compatible, neutral, incompatible. For the SRC-pd task the conditions were (from left to right): compatible direction-compatible position (CDCP), incompatible direction-compatible position (IDCP), compatible direction-incompatible position (CDIP), and incompatible direction-incompatible position (IDIP). Note that in IDCP and CDIP position and direction convey contradictory spatial information (i.e., the arrow is pointing to the opposite hemifield regarding where it is located). The response buttons were counterbalanced between participants.

Also, the SRC tasks designed in the present study allowed focusing on unresolved basic electrophysiological problems, which are specifically detailed in the following section. The remaining main sections of the introduction are devoted to age-related changes and changes related with aMCI state, respectively.

1.2 Basic psychophysiological studies: Loci of Interference and Lateralized event-related potentials (L-ERP)

A widely studied topic in the context of the Simon-type tasks was the locus of interference of the Simon effect (for an electrophysiological review on the Simon effect see Leuthold, 2011). For it, the researchers frequently analyzed the LRP, an ERP component that, through a subtraction procedure, isolates an increase of activity at electrode sites contralateral to the hand involved in preparing a movement (for a review of different ways of obtaining the LRP see Gratton et al., 1988; and for a review on its functional significance, see Eimer, 1998).

Analysis of the LRP revealed that the Simon effect occurs at the response selection stage (De Jong, Liang, & Lauber, 1994; Stürmer, Leuthold, Soetens, Schröter, & Sommer, 2002; Valle-Inclán, 1996). Moreover, the Simon task modulated the P3b component, which reflects a link between perceptual analysis and response onset (Verleger, Jaskowski, & Wascher, 2005). Specifically, P3b was slowed in the incompatible compared to the compatible condition (Leuthold and Schröter, 2006; Melara et al., 2008; Valle-Inclán, 1996; Van der Lubbe and Verleger, 2002). Likewise, P3b amplitude was found to be smaller in the incompatible than in the compatible condition (Leuthold & Schröter, 2006; Ragot, 1990; Valle-Inclán, 1996a, 1996b).

Insights on the interference loci of Simon tasks with stimuli spatially lateralized used a vertical arrangement for presenting the stimuli (e.g. Valle-Inclán, 1996, exp. 3) in

order to avoid asymmetries that would contaminate measurement of the LRP onset latency. Specifically, when the stimuli were placed in horizontal arrangement, as usually happened in the behavioural studies (for a review on behavioural studies see Lu & Proctor, 1995), the N1 ERP component (which takes place around 180 ms) (Valle-Inclán, 1996, Exp. 1) extends to central regions and thus overlaps with LRP. Such overlap does not allow a reliable measurement of the LRP.

Some researchers opted by placing a non-target stimulus in the contralateral hemifield (Valle-Inclán, 1996, exp 2; Wascher & Wauschkuhn, 1996). However, the selection between a target and a non-target stimulus result in the emergence of another parieto-occipital component, i.e. the N2 posterior-contralateral or N2pc (Luck & Hillyard, 1994; Woodman & Luck 1999). Likewise, these early studies (Valle-Inclán, 1996, exp 2; Wascher & Wauschkuhn, 1996) reported that the N2pc component was extended to central regions by volume conduction and contaminated the measured of the LRP. Consequently, in Simon tasks where the LRP is studied, the researchers opted for presenting stimuli in vertical arrangement (De Jong et al., 1994; Stürmer et al., 2002; Valle-Inclán, 1996, exp. 3) for avoiding the overlap between N2pc and LRP components that takes place at central regions and prevents a reliable measure of the LRP onset (Praamstra, 2007).

Although early studies had stated that N2pc extended and achieved central regions by volume conduction, several lines of evidence showed that N2pc and the central activity that overlapped with LRP (labelled as N2 central contralateral (N2cc) by Praamstra and Plat, 2001) were really different components. Specifically, sources reconstruction techniques showed that N2pc was generated at parieto-occipital sites and N2cc at central sites (Oostenveld, Praamstra, Stegeman, & Van Oosterom, 2001; Praamstra & Oostenveld, 2003). In addition, functional dissociation between the two

components was obtained (Praamstra, 2006; Praamstra & Oostenveld, 2003), which suggested that N2cc was involved in preventing cross-talk between the direction of the spatial attention and the manual response preparation, whereas N2pc was known to be a correlate of visuospatial processing of the target stimulus and of the suppression of the non-target stimuli (Hickey, DiLollo, & McDonald, 2009; Luck & Hillyard, 1994).

Considering that in the incompatible condition the participants have to overtake the automatic tendency of response towards the side where the attention is directed, N2cc might be modulated by the experimental condition. In fact, some studies (Stürmer & Leuthold, 2003; Leuthold & Schröter, 2006) suggested that N2cc might represent a mechanism of cognitive control in Simon tasks, even if modulations of N2cc between experimental conditions were not studied. Therefore, in the present research the SRC-p task was used (Study 1, Cespón, Galdo-Álvarez, & Díaz, 2012) for studying N2cc modulations according to the compatibility or incompatibility between the colour of the arrow (i.e., the relevant dimension) and the stimulus position (i.e., the irrelevant dimension).

Given that the N2cc overlaps with LRP at central areas in a similar temporal window, LRP and N2cc cannot be reliably measured (Praamstra, 2007). For this reason, in the SRC-p task a central stimulus was also presented for removing the common motor activity between the lateralized (i.e., the compatible and incompatible conditions) and the central stimulus (i.e., the neutral condition), through a subtraction procedure of the waveforms (Compatible minus Neutral, and Incompatible minus Neutral). This procedure (explained in the Figure 2 of the Study 1) allowed us studying N2cc modulations isolated from the motor activity. In addition, in this first study, the exact low-resolution brain electromagnetic tomography (eLORETA) (Pascual-Marqui, 2007, 2009) was used to provide support on the neural sources of N2cc, which previous

studies related with activity from the dorsal premotor cortex (Praamstra & Oostenveld, 2003). The eLORETA method and the proof of its exact zero-error localization were described by Pascual-Marqui (2007, 2009).

In addition, possible modulations of the N2pc component by the compatibility between the stimulus position and the required response were also investigated in Study 1. Since the stimuli are lateralized in the Simon task, the visuospatial attention to the target stimulus (in this case, the arrow) might play an important role and also be modulated according to the compatibility / incompatibility from the stimulus position. Critically, the studies focusing on the N2pc modulation in the Simon task were scarce and also showed inconsistent results. In fact, N2pc modulations according to the experimental condition had been observed in Valle-Inclán (1996, Exp. 2); however, subsequent studies did not find differences between the experimental conditions, and thus did not replicate the findings (Praamstra, 2006; Praamstra & Oostenveld, 2003; Van der Lubbe & Verleger, 2002).

The above discrepancies regarding N2pc modulations might have been caused by a stimulus-stimulus overlap (S-S) in the Simon task used by Valle-Inclán (1996), which was not present in the tasks used in the other mentioned studies. In Valle-Inclán (1996), the participants responded to the direction of a lateralized arrow. Thus, in addition to the overlap between the irrelevant dimension and the response, a stimulus-stimulus (S-S) overlap took place. That is, the two dimensions of the stimulus (stimulus position and direction pointed by the arrow) conveyed spatial information. It is known that the stimulus position and the direction pointed by an arrow may orient spatial attention (Klein, 2004; Klein & Ivanoff, 2011). Consequently, when the arrow was in the opposite hemifield with respect to where it was pointing, conflicting spatial information may be produced. This conflict might cause a decline in the allocation of

spatial attention to the target stimulus, which might be reflected by changes in the N2pc. Unfortunately, in the task used by Valle-Inclán (1996), it was not possible to dissociate S-S and S-R effects because the S-S incompatibility was always accompanied by S-R incompatibility and the S-S compatibility was always accompanied by the S-R compatibility, as pointed by Juncos-Rabadán, Pereiro, and Facal (2008). Therefore, the N2pc modulation could not be exclusively attributed to S-R incompatibility (Simon effect) or to S-S incompatibility.

Thus, a second study (Study 2, Cespón, Galdo-Álvarez, & Díaz, 2013) was carried out to contrast if N2pc was modulated by S-S conflict or S-R incompatibility. In this study, a sample of young participants performed the SRC-pd task (see Figure 1c). Interestingly, in this task the S-R and S-S effects could be dissociated. As outlined in previous paragraphs, in the SRC-pd task the participants responded to the colour of an arrow and ignored the position and the direction pointed by the arrow. Therefore, four experimental conditions could be distinguished: compatible direction/compatible position (CDCP), in which S-R compatibility based on the stimulus position was accompanied by S-S compatibility (S-R compatible position/S-S compatible); incompatible direction/compatible position (IDCP), in which S-R compatibility based on the stimulus position was accompanied by S-S incompatibility (S-R compatible position/S-S incompatible); compatible direction/incompatible position (CDIP), in which S-R incompatibility based on the stimulus position was accompanied by S-S incompatibility (S-R incompatible position/S-S incompatible); and incompatible direction/incompatible position (IDIP), in which S-R incompatibility based on the stimulus position was accompanied by S-S compatibility (S-R incompatible position/S-S compatible). The experimental design is summarized in the Figure 1 of the Study 2.

It was expected that visuospatial attention would be declined when S-S was incompatible (i.e. in IDCP and CDIP conditions), which would result in smaller N2pc amplitude in IDCP/CDIP than in CDCP/IDIP. The main alternative hypothesis was that N2pc was modulated by the stimulus position. In that case, a reduction of the N2pc amplitude would be expected in CDIP/IDIP regarding CDCP/IDCP conditions. Alternatively, it was possible that N2pc was modulated by the arrow direction. This possibility would be evidenced by smaller N2pc amplitude when the arrow direction was incompatible (IDCP/IDIP) than compatible (CDCP, CDIP). The three different hypotheses (modulation by S-S conflict, by stimulus position, and by direction pointed by the arrow) were graphically represented in the Study 2 (see Study 2, Figure 1c, 1d, and 1e).

On the other hand, some ERP studies proposed identical interference loci for the two S-R interferences used in the second Study (i.e., in the SRC-pd task). This interpretation was based on similarities in modulations of LRP (Masaki et al., 2000) and P3b (Galashan, Wittfoth, Fehr, & Herrmann, 2008; Masaki, Takasawa, & Yamazaki, 2000) by the two S-R interferences. However, behavioural data seems inconsistent with the notion of identical interference loci for the two irrelevant dimensions due to the following reasons: 1) The interference from the stimulus position was usually greater than the interference from the arrow direction (Wittfoth, Schardt, Fahle, & Herrmann, 2009); 2) the interference from the stimulus position was reduced with slower RTs whereas the interference from the arrow direction increased with slower RTs (Proctor, Miler, & Baroni, 2011); this result has been related to mandatory processing of the symbolic meaning of the arrow (Iani, Baroni, Pellicano, & Nicoletti, 2011; Symes, Ellis, & Tucker, 2005); 3) directional interference consistently produced a facilitation effect (Galashan et al., 2008; Masaki et al., 2000); however, the facilitation was not

consistently obtained when the irrelevant dimension was the stimulus position (for examples on the above inconsistence see Simon, 1990).

Importantly, ERP studies inferring identical interference loci for the two irrelevant dimensions might share a methodological problem: the use of a lesser proportion of incompatible than compatible and/or neutral trials. This difference can represent a problem, as that imbalance of trials between conditions results in an oddball design, which showed to modulate the P3b component (Melara, Wang, Vu, & Proctor, 2008). In addition, such imbalance predisposed to sequence effects that would increase the motor interference (Spapé, Band, & Hommel, 2011). Therefore, under the mentioned experimental conditions, ERP modulations could not be unequivocally attributed to the effect of the irrelevant dimensions or to the imbalance between conditions.

In order to resolve the above inconsistencies it was necessary to compare the two S-R incompatibilities (position and direction) using separate tasks with identical experimental parameters. Furthermore, it was necessary to take into account differences in ERP components involved on each task (i.e. N2pc and N2cc are present in the spatial tasks but not in the a task with centrally presented stimuli) as well as those parameters of the task that might modulate any of the ERP components studied (e.g. oddball designs may lead to sequence effects and both factors are related with modulations of the effect size and P3b component). Therefore, a comparison between interference from the stimulus position and interference from the direction pointed by central arrows focused the aims of another study (Study 3, Cespón, Galdo-Álvarez, & Díaz, under review, a). For it, the SRC-p and the SRC-d tasks were compared under the same experimental parameters.

1.3 Age-related differences

The fourth study (Study 4, Cespón, Galdo-Álvarez, & Díaz, in press) aimed to investigate age-related changes in ERP correlates of the cognitive processes studied in the samples of young participants. For it, samples of healthy middle-aged (50-64 years old) and elderly (65-84 years old) participants were recruited for performing the SRC-pd task. It was hypothesized that this task might be of utility in the study of the cognitive slowing and the inhibitory control theories. Regarding the cognitive slowing theory (Salthouse, 2009), we mainly focused on visuospatial (studied through N2pc) and motor (studied by means of the LRP) processes. Moreover, the reported decline in inhibitory control (Hasher & Zacks, 1988) led to focus the study on age-related differences in the motor interference (i.e., effects of the two irrelevant dimensions on the RT and the motor execution stage) and the perceptual conflict (modulations of N2pc amplitude).

It had been proposed that the main source of cognitive slowing occurred in the generation of the motor response (or motor execution stage) (Band & Kok, 2000), which was confirmed by several studies with SRC tasks (Falkenstein, Yordanova, & Kolev, 2006; Kolev, Falkenstein, & Yordanova, 2006; Roggeveen, Prime, & Ward, 2007; Yordanova, Kolev, Hohnsbein, & Falkenstein, 2004). These studies found an increase of the interval between the LRP-r onset and the overt response. Consequently, they considered the motor execution stage as a locus of age-related slowing. The SRC-pd task could be used for studying age-related slowing in the motor execution stage, besides interference related with the two irrelevant dimensions (i.e., the stimulus position and the direction pointed by the arrow).

Also, it had been proposed that visuospatial processes decline at early stages in the ageing process (Iachini, et al., 2009). Interestingly, using Simon tasks (Van der

Lubbe & Verleger, 2002) and visual search tasks (Amenedo, Lorenzo-López, & Pazo-Álvarez, 2012; Lorenzo-López, Amenedo, & Cadaveira, 2008), it was evidenced an age-related slowing in the visuospatial processes by means of the N2pc component. In the present research, the SRC-pd task was useful to study changes related with age in the visuospatial processing of the target stimulus (i.e., the arrow). In addition, it was also useful to study possible age-related changes in the conflict of spatial information conveyed by the two irrelevant dimensions, which had been studied in a sample of young participants (Cespón et al., 2013). Specifically, the perceptual conflict of spatial information conveyed by the two irrelevant dimensions (i.e., in those conditions where the arrow pointed to the opposite hemifield regarding where it was pointing), and also the motor interference (related with the two irrelevant dimensions) might be increased with age.

Some behavioural evidence about the stages when cognitive decline appears in performing a Simon task was previously obtained. Bialystok, Craik, Klein, and Viswanathan (2004), who recruited participants between 30-80 years old, observed that RT and Simon effect increased from the age of 60 years onward. Moreover, Juncos-Rabadán et al. (2008) found greater interference and increased RT in 50-59 years old relative to younger adult participants, maintenance of interference and RT in groups between 50-59 and 60-69 years old, and a subsequent decline at 70-82 years old. Juncos-Rabadán et al. (2008) linked their findings with evidence from longitudinal studies on fluid cognitive skills (Finkel, Reinolds, McArdle, & Pedersen, 2003; McArdle, Ferrer-Caja, Hamagami, & Woodcock, 2002; Willis & Schaie, 2005) that observed that ageing was associated with a decline in these cognitive abilities, starting at around 50 years old, followed by a period of relative stability and a subsequent progressive decline after 65 years old.

Despite the above behavioural evidence, the vast majority of ERP studies just compared samples of young and elderly participants whereby information about time and rate of decline in the above correlates is not available. For this reason, in Study 4 a sample of middle-aged participants (50-64 years old) was included to compare age-related changes in speed of visuospatial and motor processes as well as the above perceptual conflict and motor interference. The main hypotheses were graphically represented in Study 4, Figure 2. In general, differences among the three groups of participants were expected to appear.

1.4 Differences related with the MCI state

The SRC-pd task was implemented in a sample of participants diagnosed of amnestic Mild Cognitive Impairment (aMCI) (Study 5, Cespón, Galdo-Álvarez, and Díaz, under review, b). The aim of this study was to obtain aMCI biomarkers. The MCI is diagnosed when symptoms suggestive of AD are present but they are not sufficient to interfere in lifestyle (Grundman et al., 2004; Petersen et al., 1999). Electroencephalographic (EEG) data (Jackson & Snyder, 2008) support the hypothesis that MCI may represent a preclinical stage of AD (Petersen et al., 2009). Indeed, it has been shown that a high percentage of MCI participants develop dementia within a few years (Petersen, 2004). Therefore, MCI biomarkers would be important for allowing an early intervention and to slow down the progression from normal ageing to dementia (Levey, Lah, Goldstein, Steenland, & Bliwise 2006).

EEG and event-related potentials (ERPs) is a suitable method for obtaining MCI biomarkers, since it is a widely diffused, non-invasive and relatively inexpensive procedure (Rossini et al., 2006). In addition, the high temporal resolution of the EEG technique is also especially useful for addressing the speed of the cognitive processes in

order to establish differences in brain electrical measures between MCI and normal ageing. As pointed earlier in the Introduction, behavioural studies suggested that visuospatial (Iachini et al., 2009) and response-related processes (Castel et al., 2007) were affected at very early stages in the progression from the normal ageing to the dementia. Therefore, it is reasonable to obtain aMCI biomarkers focused on ERP correlates of visuospatial (N2pc) and response-related (LRP) processes, which were not investigated in previous studies with samples of MCI participants.

Several studies, using SRC tasks, reported slowing and declined inhibitory control in MCI participants (Castel et al., 2007; Wylie Ridderinkhof, Eckerle, & Manning, 2007). In the present study, the use of the SRC-pd task allowed studying, besides of the speed of response, the interference from two irrelevant dimensions (stimulus position and arrow direction). Also, as mentioned in the previous section, the motor execution stage was reported to represent the main source of slowing in elderly persons (e.g. Kolev et al., 2006). Therefore, the increased slowing in RTs observed in aMCI participants might affect this stage. This effect would be revealed by an additional prolongation of the response execution stage, which was measured using the LRP-r onset. Also, a recent transcranial magnetic stimulation (TMS) study suggested an impairment of the motor cortex in the MCI participants (Tsutsumi et al., 2012). For this reason, it was important to study the LRP-r amplitude because it might be an indicator of the resources allocated to the implementation of the response.

On the other hand, Iachini et al. (2009) carried out an exhaustive revision on changes related with age and Alzheimer`s disease in visuospatial abilities. A conclusion of this review was that visuospatial deficits are expected to appear in early stages in the progression from normal ageing to AD. Taking into account that evidence, N2pc

parameters (i.e., latency and amplitude) were also used to test the possibility of obtaining correlates and possible biomarkers of the MCI state.

1.5 Summary of the main aims and hypotheses

Firstly, in samples of young participants, it was intended: 1) to study modulations of the N2cc and N2pc components in the Simon-type tasks with lateralized stimuli and 2) comparing the effects of interference produced by lateralized stimuli (i.e., interference from the stimulus position, in the SRC-p task) and by central arrows (i.e., interference from the direction pointed by the arrow, in the SRC-d task).

In the Study 1 it was hypothesized that the N2cc component represent a correlate of the activity involved in monitoring the selection of the correct response by preventing the cross-talk between the direction of the spatial attention and the manual response preparation. According to this hypothesis, it would be expected a greater N2cc activity in the incompatible than in the compatible condition since a greater activity for preventing the above "cross-talk" would be necessary in the incompatible condition, where the side of the required response is opposite regarding the direction of the spatial attention. Also, it was expected obtaining a functional dissociation, in the SRC-p task, between N2cc and N2pc components since N2pc would not be modulated by stimulus position but by the stimulus-stimulus conflict, which was investigated in the Study 2 by means of the SRC-pd task.

According to behavioural differences in the pattern of results for position and direction interferences, in the Study 3 (in which SRC-p and SRC-d tasks were compared), it was expected to find out electrophysiological differences between the two irrelevant dimensions in P3b and / or LRP components because behavioural studies revealed that the interference from the stimulus position is greater than the interference

from the arrow direction and, in addition, the interference from the stimulus position affect to faster RT than the direction interference.

Secondly, the SRC-pd task was implemented in samples of healthy middle-aged and elderly participants and in participants diagnosed of aMCI. Firstly, it was aimed studying age-related differences in the context of the cognitive slowing (delays in visuospatial attention to the target stimulus and in motor execution) and inhibitory control (motor interference and perceptual conflict) theories. Therefore, the Study 4 examined the existence of differences in the mentioned processes. Specifically, it was expected a progressive cognitive slowing in the correlates of the studied processes. In addition, motor interference and perceptual conflict were expected to increase with ageing. On the other hand, the sample of aMCI participants was used, in the Study 5, for studying possible ERP correlates of visuospatial and motor processes in order to obtain aMCI biomarkers.

2. STUDIES

2.1 Study 1 (Estudio 1)

Cespón, J., Galdo-Álvarez, S., & Díaz, F. (2012). The Simon effect modulates N2cc and LRP but not the N2pc component. *International Journal of Psychophysiology 84*, 120-129.

Estudios previos mostraron que la disposición horizontal de los estímulos en tareas tipo Simon da lugar a la aparición de tres componentes diferentes: Potencial de preparación lateralizado (PPL), N2 posterior contralateral (N2pc) y N2 central contralateral (N2cc). Aunque N2cc podría jugar un papel fundamental en tareas Simon, dada su relación con la prevención de respuestas basadas en la posición del estímulo, no se había investigado previamente la posible modulación de N2cc en función de las condiciones experimentales en dichas tareas, debido al solapamiento de los componentes N2cc y PPL en regiones y ventana temporal similares. El objetivo del presente estudio era investigar cómo el efecto Simon modula N2pc, N2cc y PPL. Para este propósito, los participantes fueron instruidos a responder a una flecha en función de su color. La tarea constaba de tres condiciones, dependiendo de la compatibilidad entre la posición del estímulo y la respuesta requerida: posición compatible (CP), posición incompatible (IP), y posición neutral (NP). Los resultados mostraron un retraso en la latencia de pico del componente PPL en la condición IP con respecto a las condiciones CP y NP. Se sustrajeron los trazados ante los estímulos en posición lateralizada menos neutral (trazados L-NP) para eliminar la actividad motora común y aislar los componentes N2cc y N2pc en las condiciones lateralizadas. La amplitud de N2cc en las ondas L-NP fue mayor en la condición IP que en la condición CP, lo cual fue consistente con el mayor esfuerzo requerido para monitorizar la selección de la respuesta correcta en la primera condición. Además, el análisis mediante eLORETA reveló mayor actividad premotora entre 150-200 ms en las condiciones IP y CP que en la condición NP, lo cual fue atribuido al componente N2cc, presente en las condiciones IP y CP. Además, en este estudio se obtuvo evidencia para la disociación funcional entre los componentes N2cc y N2pc ya que N2cc, pero no N2pc, fue modulado por las condiciones experimentales.

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The Simon effect modulates N2cc and LRP but not the N2pc component

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ABSTRACT

Previous studies have reported that the horizontal arrangement of the stimuli in Simon tasks elicits three different components: LRP, N2pc and N2cc. Although N2cc may play a key role in Simon tasks, as it is involved in preventing responses based on stimulus position, modulation of the N2cc component according to the experimental conditions has not previously been investigated because of N2cc/LRP overlap in similar regions and temporal window. The aim of the present study was to investigate how the Simon effect modulates N2pc, N2cc and LRP components. For this purpose, participants were asked to respond to an arrow according to its colour. Three conditions, which depended on the congruency between stimulus position and the required response, were analysed: compatible position (CP), incompatible position (IP), and neutral position (NP). The LRP peak latency was delayed in IP with respect to CP and NP conditions. Lateralized minus neutral position (L–NP) subtractions were carried out to remove the common motor activity and isolate the N2cc and N2pc components in the lateralized conditions. The N2cc amplitude in L − NP waveforms was larger in IP than in CP, in accordance with the greater effort required to monitor selection of the correct response in the first condition. eLORETA analysis also revealed greater premotor activity at 150–200 ms in IP and CP, than in NP, which was attributed to the N2cc component present in IP/CP conditions. Evidence of functional dissociation between N2pc and N2cc components was obtained, because N2cc, but not N2pc, was affected by the experimental conditions.

1. Introduction

The Simon task is a stimulus–response compatibility task (SRC) (Kornblum and Stevens, 2002), in which participants must respond to spatially lateralized stimuli by pressing one of two buttons. The response buttons are also lateralized in the same spatial arrangement as the stimuli, with the position of the stimuli being irrelevant to the task. In those cases in which the required response is on the opposite side to the stimulus (incompatible condition), a type of interference known as the Simon effect is produced (for reviews see Leuthold, 2011; Lu and Proctor, 1995; Simon, 1990). The interference is manifested by a slower reaction time (RT) in the incompatible condition than in the compatible condition, in which the response side is ipsilateral with respect to the stimulus position.

Analysis of the lateralized readiness potential (LRP) revealed that the Simon effect occurs during the response selection stage (Valle-Inclán, 1996). The LRP is an event-related potential (ERP) associated with motor activity, and it allows distinction between interference produced during motor stages and interference produced during perceptual stages of processing (Gratton et al., 1988; for a review of different ways of obtaining LRP, and its functional significance, see Eimer, 1998). However, it has been shown that the location of the stimuli produces lateralized modulations that overlap with motor activity.

When the stimuli are presented in a horizontal arrangement, the eccentric location induces asymmetry in the exogenous ERP N1 (at around 180 ms) (Valle-Inclán, 1996, Experiment 1). This asymmetry can extend to central regions, thus affecting measurement of the LRP. To avoid such asymmetry, some researchers have presented a non-target stimulus in the contralateral hemifield (Valle-Inclán, 1996, Experiment 2). However, such stimulus configuration requires visuospatial selection of the relevant stimulus, which elicits a component named N2 posterior contralateral (N2pc). N2pc is observed at parieto-occipital electrode sites contralateral to the stimulated hemifield, between 200 and 300 ms, and represents visuospatial processing of the relevant stimulus (Luck and Hillyard, 1994; Woodman and Luck, 1999, 2003). N2pc may be accompanied by a deflection of the same polarity at central electrodes (N2 central contralateral— N2cc), which would hinder evaluation of the motor activity (Valle-Inclán, 1996 Exp. 2; Wascher and Wauschkuhn, 1996). N2cc has been suggested to play an important role in preventing cross-talk between the direction of the spatial attention and the manual response preparation (Praamstra, 2006, 2007; Praamstra and Oostenveld, 2003).

The N2cc wave was first interpreted as volume conduction from posterior areas, i.e. from N2pc activity (Valle-Inclán, 1996 Experiment 2; Wascher and Wauschkuhn, 1996). However several studies have shown that N2pc and N2cc are different components. Using a

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biophysical model, Oostenveld et al. (2001) showed that the amplitude recorded at central electrodes in the temporal window of the N2pc was too large to be explained by volume conduction from N2pc sources. Also, in the latter and other studies (Praamstra and Oostenveld, 2003; Praamstra and Plat, 2001), the use of source reconstruction techniques enabled identification of activity peaks at central and at parieto-occipital regions, thus indicating the existence of two different components. Moreover, Van der Lubbe et al. (2001) showed that lateralization at central electrodes did not occur parallel to the N2pc, suggesting different sources of activity for central and parieto-occipital waves. Finally, some studies have shown functional dissociation between N2pc and N2cc, since both were differentially affected by experimental manipulation of the tasks (see Praamstra, 2006; Praamstra and Oostenveld, 2003).

The scalp distribution of the N2cc, as well as the conditions under which it was elicited, suggest that N2cc is associated with activation of the dorsal premotor cortex (dPM) (see Praamstra and Oostenveld, 2003). In fact, the dPM is involved in selection of movements according to learned associations in spatial tasks (Rushworth et al., 2003). In addition, visual and motor signals were found to interact in the dPM (Wise et al., 1996, 1997; for a review on dPM, see Abe and Hanakawa, 2009).

In order to prevent overlap between N2pc/N2cc and the motor activity, some researchers have used a vertical arrangement of stimuli and responses (de Jong et al., 1994; Stürmer et al., 2002; Valle-Inclán, 1996, Experiment 3). Using this arrangement, N2cc and N2pc are not elicited. Nonetheless, in our opinion (see also Leuthold, 2011), it is important to examine the N2cc in the Simon task, as it may reflect a mechanism of cognitive control.

The present study involved a Simon task with lateralized stimuli. The positions of the stimuli were compatible (compatible position, CP), incompatible (incompatible position, IP) or central (neutral position, NP) with respect to the required response. The stimuli were presented in a horizontal arrangement to determine whether the location modulated only motor processes (analysed via LRP), as maintained in previous studies (de Jong et al., 1994; Stürmer et al., 2002; Valle-Inclán, 1996, Experiment 3), or also other cognitive processes, specifically the visuospatial processing of the relevant stimulus (which has been related to N2pc) and the cognitive control that prevents execution of the response based on stimulus position (which has been related to N2cc).

In order to clarify the existence of these effects, two procedures were carried out to isolate the N2cc and N2pc components from the motor activity. Firstly, the NP waveform was subtracted from the CP and the IP waveforms, as central stimuli elicit LRP but not N2cc and N2pc components. Also, analyses were carried out to discount the possibility that the differences in motor activity between lateralized and NP conditions affected the lateralized minus neutral position (L − NP) waveforms. Secondly, the CP and the IP conditions were compared with the NP condition using eLORETA source analyses (Pascual-Marqui, 2007, 2009).

In the waveforms in which N2cc and N2pc were isolated (i.e. when the motor activity is subtracted), we expected to find a larger N2cc amplitude in the IP than in the CP condition, as the cognitive control for monitoring selection of the response based on the relevant dimension (the colour of the arrow) should be greater in the IP than in the CP condition. On the basis of e-LORETA estimations, we expected to find higher activity in premotor areas during the N2cc time interval in the CP and IP than in the NP. We did not expect to find any differences in the N2pc component between CP and IP, as the Simon effect does not appear to take place in the visuospatial processing of the relevant stimulus. Therefore, another aim of the present study was to obtain new evidence of the functional dissociation between N2pc and N2cc components. Finally, with respect to the modulation of the motor activity by the stimulus position, we expected to find longer LRP peak latency in the IP than in the CP and NP conditions, consistent with the slower RT in the IP condition.

2. Methods

2.1. Participants

Nineteen participants (14 women, 5 men) between 19 and 28 years old (mean age: 21 years old) were recruited from the local university population. Four participants (3 women) were not included in some of the ERP analyses because of an insufficient number of artefact-free epochs in some of the conditions. The participants volunteered to take part in the study and were paid for participating. The study received prior approval by the local ethical review board. Eighteen of the participants were right-handed and one was ambidextrous (evaluated by the Edinburgh Handedness Inventory: Oldfield (1971)). All participants had normal or corrected to normal vision and none had any history of neurological or psychiatric disorders.

2.2. Stimuli

A series of upward-pointing red or blue arrows was displayed on the screen against a black background, either on the left or on the right side of a white central cross for both compatible and incompatible conditions. In the neutral condition, the stimuli were upward-pointing red or blue arrows placed on the central cross. The arrow stimuli subtended 2.87° × 1.72° (height × width) of the visual field. In the compatible and incompatible conditions, the visual stimuli were presented 3.1° (visual angle) from the centre of the screen at the centre of the stimulus. The lateralized (CP and IP) and central stimuli were presented in parafoveal and foveal regions respectively (see Bargh and Chartrand, 2000), although differences in stimuli processing due to this eccentricity were not expected (Galashan et al., 2008; Mancebo-Azor et al., 2009). In the compatible and incompatible conditions, a geometric figure (two superimposed orthogonal bars, with the vertical bar longer than the horizontal bar, of similar size and eccentric position as the arrow) appeared in the opposite hemifield to prevent exogenous lateralization in the electroencephalogram (EEG) (see Fig. 1).

2.3. Procedure

The participants were asked to direct their gaze towards the central cross during the task, and were instructed to respond to the colour of the arrow as quickly as possible by pressing one of the two buttons assigned to each colour. They were also instructed to ignore the position of the arrow. A cross appeared in the centre of the screen and remained in view throughout the task. The response buttons were arranged horizontally and were pressed with the corresponding hand (right or left) so that when the arrow was in the central position, there was no overlap between the position and the dimension of the response, and the trials were therefore considered neutrals. In each block, each of six possible types of stimuli, grouped in three conditions with the same number of trials (80 per condition) were presented at random: compatible position (CP, the response required was ipsilateral to the hemifield of appearance of the target), incompatible position (IP, the required response was contralateral to the hemifield of the appearance of the target), and neutral position (NP, as described above, there was no overlap between stimulus position and response). The arrows were presented for 100 ms, with inter-trial intervals of 2000 ms. The possibility of ocular movements towards the position of the target when this was presented at eccentric locations was minimised by the short duration of presentation of the stimuli and the simultaneous presentation of the non target stimulus in the contralateral hemifield (see Abrahamse and Van der Lubbe, 2008).

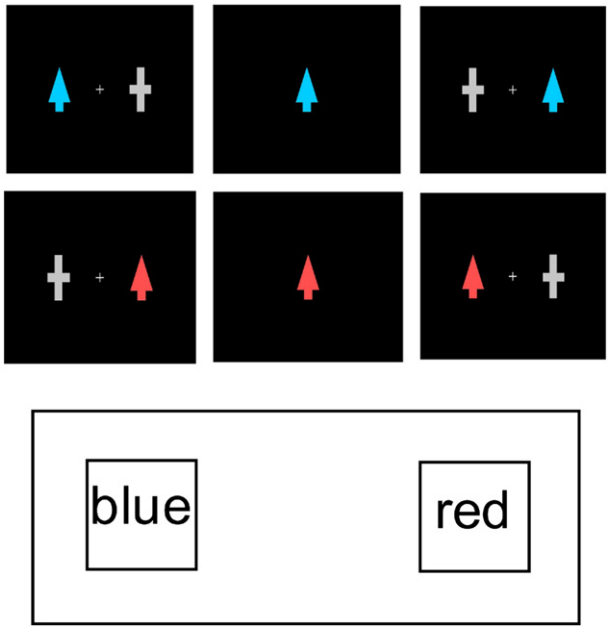

Fig. 1. The task comprised six types of stimuli grouped in three conditions according to the position of the stimulus in relation to the hand making the response. The participants were instructed to respond by pressing the button on the left, with their left hand, when a blue arrow appeared, and the button on the right, with their right hand, when a red arrow appeared, while ignoring the stimulus position. The conditions presented from left to right were: compatible position (CP), neutral position (NP) and incompatible position (IP).

During the task, participants were seated in a comfortable chair in a dimly lit, sound-attenuated, electrically shielded chamber. The experiment included a practice block of 16 trials and two experimental blocks of 120 trials each, with a resting interval of 90 s between blocks.

The trials were counterbalanced so that half of the participants were instructed to respond by pressing the button on the left with their left hand, in response to the blue arrow, and the button on the right with their right hand, in response to the red arrow, whereas the other participants were given instructions to respond in the opposite way.

2.4. Recordings

Electroencephalographic activity was recorded at 49 active electrode sites, inserted in an electrode cap (Easycap, GmbH) in accordance with the 10-10 International System: AFz, AF3, AF4, AF7, AF8, Fz, F3, F4, F5, F6, F7, F8, FCz, FC1, FC2, FC3, FC4, FT7, FT8, FT9, FT10, Cz, C1, C2, C3, C4, C5, C6, T7, T8, CPz, CP3, CP4, TP7, TP8, TP9, TP10, Pz, P3, P4, P7, P8, P9, P10, PO7, PO8, Oz, O1 and O2. The EEG signal was passed through a 0.01–100 Hz analogue bandpass filter, and was sampled at 500 Hz. The reference electrode was placed on the tip of the nose and the ground electrode at Fpz. Simultaneously to EEG recordings, ocular movement (EOG) recordings were obtained with two electrodes located supra- and infraorbitally to the right eye (VEOG) and another two electrodes at the external canthus of each eye (HEOG). All impedances were maintained below 10 kΩs. After signal storage, ocular artefacts were corrected off-line by use of the algorithm proposed by Gratton et al. (1983); the EEG was then segmented separately for each condition and manual response (in order to study Lateralized event-related potentials), and 1000-ms epochs (200 ms pre-stimulus baseline) aligned to the onset of stimulus presentation. The signal was passed through a 0.01–30 Hz digital band-pass filter. Epochs with signals exceeding ±100 μV were automatically rejected, and all remaining epochs were inspected individually to identify those still displaying artefacts; the artefacted epochs were also excluded from subsequent averaging. The mean number of epochs (± Standard Deviations) for each condition was as follows: Compatible trials, 70 (±8.2); Incompatible trials, 65.7 (±9.9), and Neutral trials 72.67 (±7.7). Epochs were then corrected to the mean voltage of the 200-ms pre-stimulus recording period (baseline).

2.5. Data analysis

Trials with incorrect responses or RTs outside the 100–1000 ms range were considered incorrect and were excluded from the subsequent analysis. The RTs and percentages of incorrect responses were analysed. Interference was considered as the difference between the RT in the IP condition and the RT in the CP condition. To determine if the magnitude of the interference, or of any possible facilitation, depended on the speed of response, three distributional analyses (DA) of the RTs were carried out (Ratcliff, 1979): IP–CP; IP–NP; and NP–CP. For this, the RTs were ordered on the basis of their speed, and for each participant the RTs at the 4 Quintile Intersection Points that divided the distribution into 5 equal parts (quintiles) were selected.

Lateralized event-related potentials (L-ERPs) were calculated as the differences in contralateral and ipsilateral activation at homologous electrodes (C3/4 for analyses related to the N2cc/LRP complex; P7/8 and PO7/8 for the analyses related to N2pc).

The operation for calculating the N2pc component can be summarized by the formula $[(P7/PO7 - P8/PO8)_{\text{right-hemifield target stimulus}} + (P8/PO8 - P7/PO7)_{\text{left-hemifield target stimulus}}]/2$ (see Wascher and Wauschkuhn, 1996). N2pc latency and amplitude were determined as the maximum peak with respect to baseline in the 210–280 ms interval in the CP and IP conditions, based on inspection of the grand average and similar to the temporal window considered by previous reports (e.g. Woodman and Luck, 1999).

The operation for obtaining the N2cc/LRP complex can be summarised by the formula: $[(C4 - C3)_{\text{left-hand movements}} + (C3 - C4)_{\text{right-hand movements}}]/2$ (see Coles et al., 1988). Therefore, to obtain a waveform for the NP condition, the N2cc/LRP complex was calculated in relation to the response hand and not in relation to the hemifield of stimulus presentation. A first interval between 210 and 280 ms was considered, based on inspection of the grand averages, to determine the peak latency and amplitude of N2cc/LRP complex in the CP, IP and NP conditions. Absolute values were used in this analysis. We adopted the term "N2cc/LRP complex" although the N2cc component is not present in the NP condition. In a second interval, the peak latency of the LRP was measured in the CP, NP and IP conditions at between 300 and 500 ms with respect to the stimulus presentation. In this second interval the motor activity was expected to be free of overlap from the N2cc component, according to the N2cc latency reported in previous studies, i.e. at about 150–200 ms (Leuthold and Schröter, 2006). The HEOG for the 3 conditions is shown in order to discount the possibility of differences in ocular movements in the lateralized conditions (CP and IP) with respect to the NP.

N2pc and N2cc components were isolated from the motor activity related to the response through the next procedure. Firstly, the direct waveforms were obtained in each condition (CP, IP, and NP). Secondly, the following subtractions were carried out at each electrode site: $CP_{\text{left-hand movements}} - NP_{\text{left-hand movements}}$; $CP_{\text{right-hand movements}} - NP_{\text{right-hand movements}}$; $IP_{\text{left-hand movements}} - NP_{\text{left-hand movements}}$; and $IP_{\text{right-hand movements}} - NP_{\text{right-hand movements}}$. Thus, the common motor activity in CP and IP with respect to NP was removed (this step resulted in the waveforms depicted in Fig. 2.1) (Fig. 2). Thirdly, the resulting waveforms ($CP\text{-}NP_{\text{left-hand movements}}$, $CP\text{-}NP_{\text{right-hand movements}}$, $IP\text{-}NP_{\text{left-hand movements}}$, and $IP\text{-}NP_{\text{right-hand movements}}$) were computed (separately for the CP-NP and for the IP-NP waveforms) by the following procedure: $[(C4 - C3)_{\text{left-hemifield target stimulus}} + (C3 - C4)$

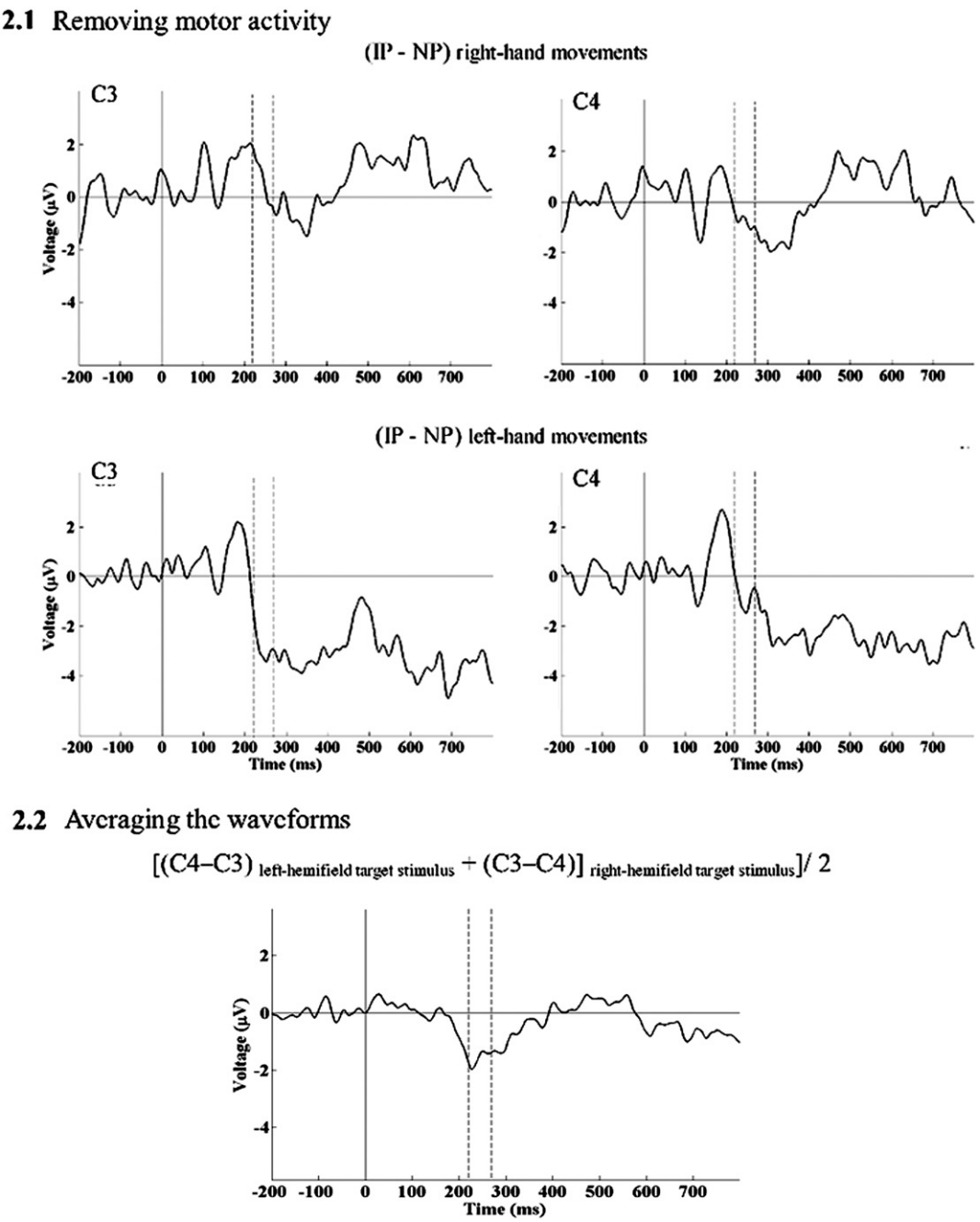

Fig. 2. The procedure for obtaining the L − NP is graphically represented for the IP condition (Fig. 2.1). In the first set of operations the "IP-NP" subtraction was carried out for the stimulus-related waveforms on each electrode individually. In this step the motor activity between IP and NP was removed in the N2cc interval resulting in a waveform around the baseline in the contralateral electrodes to the hand that executes the response (C3 for right hand movements and C4 for left hand movements). Moreover, the subtraction resulted in negative waveforms at electrodes contralateral to the stimulus presentation (C3 for stimuli presented in the right hemifield and C4 for stimuli presented in the left hemifield), which represents the activity related to N2cc (Fig. 2.2). In the second set of operations, the activity at C3 and C4 electrodes was averaged through the LRP formula (in the text) in order to obtain a single waveform related to N2cc activity on each condition. The same procedure was used to subtract the motor activity in the CP condition.

$_{\text{right-hemifield target stimulus}}]/2$, to obtain the N2cc in the lateralized-neutral position waveforms (L − NP) (see Figs. 2.1 and 4.1), and $[(P8 - P7)_{\text{left-hemifield target stimulus}} + (P7 - P8)_{\text{right-hemifield target stimulus}}]/2$, to obtain the N2pc in the L − NP waveforms (see Fig. 4.2). The N2cc and N2pc peaks in these L − NP waveforms were determined in a temporal window of 150–300 ms, based on inspection of the grand averages.

Analyses were carried out with exact low-resolution brain electromagnetic tomography (e-LORETA) software (publicly available free academic software, at http://www.uzh.ch/keyinst/loreta.htm), which estimated the source of activity underlying the brain activity recorded at the 49 scalp electrodes. The analysis compared the brain activity in the CP, IP and NP conditions in eight temporal intervals of 50 ms, from 150 to 550 ms post-stimulus. On the basis of the distribution of the scalp-recorded electric potential, eLORETA software was used to compute the cortical three-dimensional distribution of current density. The eLORETA method is a distributed, linear-weighted minimum norm inverse solution. The weights endow the tomography with the property of exact localization to test point sources, accurately yielding located images of current density, albeit

with low spatial resolution (i.e. neighbouring neuronal sources will be highly correlated). The method and the proof of its exact zero-error localization property are described by Pascual-Marqui (2007, 2009).

The related LORETA and sLORETA tomographic methods (Pascual-Marqui, 2002; Pascual-Marqui et al., 1994) have been validated in several studies combining LORETA with other more established location methods such as functional Magnetic Resonance Imaging (fMRI, Mulert et al., 2004; Vitacco et al., 2002), structural MRI (Pizzagalli et al., 2004; Worrel et al., 2000; Zumsteg et al., 2005), Positron Emission Tomography (PET, Dierks et al., 2000; Pizzagalli et al., 2004; Zumsteg et al., 2005) and invasive implanted electrode recordings (Zumsteg et al., 2006). The results of these studies also validate eLORETA, owing to its improved localization properties. The intracerebral volume is partitioned in 6239 voxels at a spatial resolution of 5 mm. The eLORETA images therefore represent the electric activity at each voxel in neuroanatomical Montreal Neurological Institute (MNI) space as the exact magnitude of the estimated current density. Anatomical labels, Brodmann areas and MNI coordinates are also reported.

2.6. Statistical analysis

With the aim of determining possible behavioural differences related to the experimental conditions, repeated measures ANOVAs were carried out with an within-subject factor, Condition (three levels: CP, IP and NP), for the RTs and for the percentage of errors (PE). In addition, the Kolmogorov-Smirnov test was carried out with the PE in order to test whether the parametric assumptions were fulfilled. The PE was analysed by non parametric tests (Friedman and Wilcoxon tests). One-sample Student's t tests were applied to each quintile intersection point (q1, q2, q3, q4), with the aim of determining if the interference (IP–CP and IP–NP) and facilitation effect (NP–CP) were significant in each. A repeated measures ANOVA was also carried out with one within-subject factor: Quintile Intersection Points (four levels: q1, q2, q3, q4), with the aim of determining if the magnitude of the interference or facilitation varied in relation to the speed of response.

Repeated measures ANOVAs with one within-subject factor, Condition (three levels: CP, IP and NP) were applied to N2cc/LRP complex and LRP peak latencies and amplitudes. Repeated measures ANOVAs with two within-subject factors, Condition (two levels: CP and IP) and Electrode (two levels: P7/8 and PO7/8), were carried out for the amplitude and latency of the N2pc.

For the lateralized (CP and IP) minus neutral position waveforms (L − NP), repeated measures ANOVAs for peak latency and peak amplitude were carried out with two within-subject factors, Condition (two levels: CP–NP and IP–NP) and Electrode (two levels: C3/4 and P7/8). These analyses are carried out within the same repeated measures ANOVA, with the aim of revealing the functional dissociation between the N2pc (measured at P7/8 electrode sites) and N2cc components (measured at C3/4 electrode sites). Furthermore, one-sample t-tests were applied to the average amplitude in ±25 ms around the maximum negative peak, observed in the CP condition in a 150-300 ms temporal window, to determine whether the N2cc was significant in the CP condition (see Fig. 4.1). In order to demonstrate that N2cc was constituted by activity in the hemisphere contralateral to the hemifield where the stimulus was presented (N2cc activity) and not by activity contralateral to the hand that executed the response (which would represent motor activity not subtracted), a one-sample *t*-test was applied to the waveforms of the set of subtractions depicted in Fig. 2.1. The t-tests were applied to the average amplitude in the temporal window where the N2cc was larger in the IP condition (220–270 ms, see Fig. 4.1).

The Greenhouse–Geisser ε correction for the degrees of freedom was performed where necessary, and the corresponding α levels are provided. When the ANOVAs revealed significant effects due to the factors and their interactions, post-hoc multiple pairwise comparisons of the mean values were carried out (with Bonferroni corrections).

The eLORETA software was used to perform voxel-by-voxel within-subject comparisons for each of the 50 ms intervals analysed (see Data analysis), in order to identify possible differences in the brain electrical activity between pairs of conditions (CP and NP; IP and NP; CP and IP). Non-parametric statistical analysis of functional eLORETA images (Statistical non-Parametric Mapping; SnPM) was performed with a log-F-ratio statistic for paired groups. The results correspond to maps of log-F-ratio statistics for each voxel, for corrected $p<0.05$. As explained in the review by Nichols and Holmes (2002), the SnPM methodology corrects for all multiple comparisons and does not require any assumption of Gaussian distribution.

3. Results

3.1. Behavioural measures

The repeated measures ANOVA (Condition) revealed a significant effect of the factor on the RT ($F(2,36)=53.0$, $p<0.001$), as the RT was shorter in CP trials ($p<0.001$) and NP trials ($p<0.001$) than in IP trials, and on the percentage of errors (PE) ($F(2,36)=18.6$, $p<0.001$), as the PE was greater in IP trials than in CP trials ($p=0.002$), and NP trials ($p<0.001$) (see Table 1). Although the assumptions for parametric testing were fulfilled for the CP and IP conditions, they were not fulfilled for the NP condition (for the CP condition, (KS (19) = 0.185, $p=0.085$), for the IP condition, (KS (19) = 0.121, $p=0.200$); and for the NP condition, (KS (19) = 0.121, $p=0.014$), so that non parametric tests were carried out. The Friedman test revealed significant differences between experimental conditions ($F(2,19)=14.00$, $p=0.001$). The Wilcoxon test revealed that the significant differences were between the IP and the CP condition ($Z=-3.059$, $p=0.002$) and between the IP and the NP condition ($Z=-3.501$, $p<0.001$).

With regard to the magnitude of the interference (in IP-CP: q1 = 36 ms; q2 = 43 ms; q3 = 43 ms; q4 = 40 ms; and in IP-NP: q1 = 43 ms; q2 = 42 ms; q3 = 43 ms; q4 = 50 ms), the one-sample t-tests revealed that the Simon effect was significant for the 4 quintile intersection points in IP – CP: q1 ($t(18)=7.22$, $p<0.001$); q2 ($t(18)=8.53$, $p<0.001$); q3 ($t(18)=8.21$, $p<0.001$) and q4 ($t(18)=4.76$, $p<0.001$), as well as in IP – NP: q1 ($t(18)=6.84$, $p<0.001$); q2 ($t(18)=8.44$, $p<0.001$); q3 ($t(18)=6.29$, $p<0.001$) and q4 (t (18)

Table 1
Mean and standard deviation, for each Condition (Compatible Position (CP), Neutral Position (NP), and Incompatible Position (IP)) of Reaction Time (in milliseconds); Percentage of Errors (PE); peak latency and peak amplitude of N2cc/LRP complex at C3/C4; peak latency of the LRP at C3/C4. For CP and IP conditions: N2pc peak latency and peak amplitude at P7/P8. Mean and standard deviation of Lateralized minus Central Stimulus subtractions (L − NP) (Compatible Position minus Neutral Position (CP − NP) and Incompatible Position minus Neutral Position (IP − NP)) of N2cc peak latency and peak amplitude at C3/C4; N2pc peak latency and peak amplitude at P7/P8.

Condition	CP	NP	IP
RT	408 (41)	401 (46)	444 (43)
PE	4.9 (3.5)	3.3 (3.0)	11.0 (6.9)
N2cc/LRP peak latency	246 (19.5)	238 (22.1)	238 (22.2)
N2cc/LRP peak amplitude	2.9 (1.3)	2.4 (1.3)	1.1 (0.8)
LRP peak latency	358 (39)	349 (44)	415 (59)
N2pc peak latency	244 (18.9)		238 (13.9)
N2pc peak amplitude	−3.8 (2.6)		−4.1 (2.9)
N2cc peak latency (L − NP)	223.3 (33.5)		250.2 (40.9)
N2cc peak amplitude (L − NP)	−1.4 (1.3)		−3.1 (1.7)
N2pc peak latency (L − NP)	240.1 (40.5)		232.5 (18.7)
N2pc peak amplitude (L − NP)	−4.4 (3.1)		−4.3 (3.4)

= 5.52, p<0.001). The repeated measures ANOVA (Quintile Intersection Point) did not reveal any significant factor effects. With regard to the magnitude of facilitation (NP-CP: q1 = -7 ms; q2 = 1 ms; q3 = 1 ms; q4 = -10 ms), neither the t tests nor the repeated measures ANOVA (Quintile Intersection Points) revealed any significant effect.

3.2. ERP

With respect to the N2cc/LRP complex peak latency, the repeated measures ANOVA (Condition) did not reveal any significant effect of the factor. With respect to the N2cc/LRP complex peak amplitude, the repeated measures ANOVA (Condition) revealed a significant effect of the factor ($F(1,14) = 26.3$, $p<0.001$), as the amplitude was larger in the CP than in the IP condition ($p<0.001$) and in the NP than in the IP condition ($p<0.001$) (see Table 1 and Fig. 3.1).

The repeated measures ANOVA (Condition) for the LRP peak latency (measured at the second interval, 300–500 ms: see Data analysis) revealed a significant effect of the factor ($F(2,28) = 8.0$, $p = 0.002$), as the latencies were shorter in the CP than in the IP condition ($p = 0.048$) and shorter in the NP than in the IP condition ($p = 0.013$) (see Table 1 and Fig. 3.1). Note that between 300 and 500 ms, the motor activity did not overlap with the N2cc component since at this time in L − NP subtractions, the waveforms (for CP-NP and IP-NP) are around baseline (see Fig. 4).

The repeated measures ANOVA (Condition × Electrode) for the N2pc latency did not reveal any significant effect. With regard to the N2pc amplitude, the repeated measures ANOVA (Condition × Electrode) revealed a significant effect due to the Condition × Electrode interaction ($F(1,14) = 6.1$, $p = 0.027$), as the amplitude was larger at P7/8 than at PO7/8 ($p = 0.006$) in the CP condition.

The repeated measures ANOVA (Condition × Electrode) for the peak latencies of lateralized minus neutral position (L − NP) waveforms did not reveal any significant effect. The repeated measures ANOVA (Condition × Electrode) for the amplitudes of L − NP waveforms revealed a significant effect of Electrode ($F(1,14) = 14.2$, $p = 0.002$), as the amplitude was greater in the P7/8 than in the C3/4 electrode pair ($p = 0.002$). An effect of the Condition × Electrode interaction was also revealed ($F(1,14) = 7.8$, $p = 0.014$), as the amplitude was greater in the IP than in the CP condition at the C3/4 electrode pair ($p = 0.004$), while there were no such differences at the P7/8 electrode pair.

The one-sample *t*-test for the mean amplitude around the larger negative peak in the CP condition of the L − NP waveforms revealed a significant difference ($t(14) = -5.845$, $p<0.001$). For the N2cc time interval (220–270 ms), the one sample t-tests also revealed that N2cc in the incompatible L − NP waveform was constituted by activity in the hemisphere contralateral to the hemifield where the stimulus was presented (N2cc activity) and not by activity contralateral to the hand that executed the response, as there were no significant differences from zero at the electrodes contralateral to the hand movement: $IP_{\text{left-hand movements}} - NP_{\text{left-hand movements}}$ at C4 ($t(14) =$

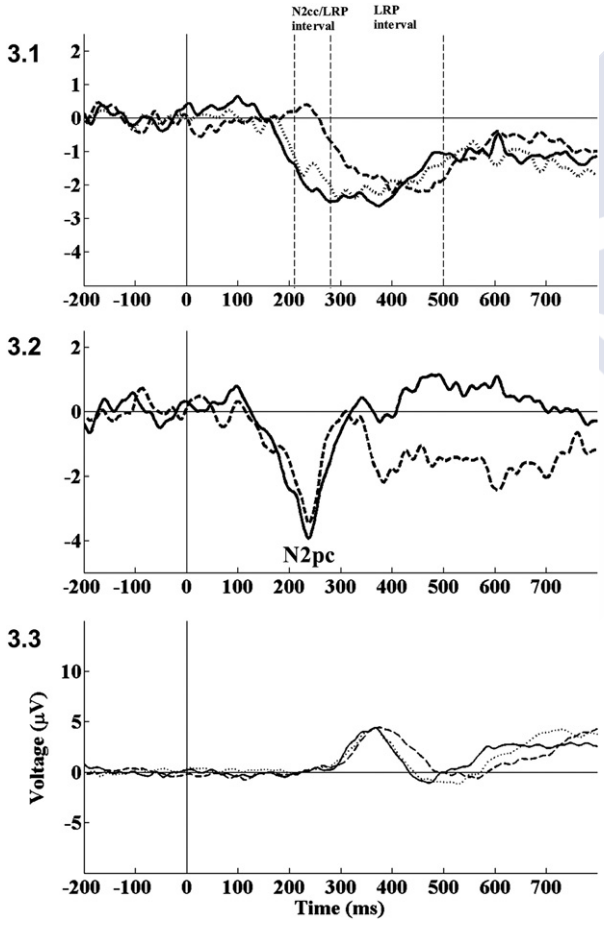

Fig. 3. N2cc/LRP (first interval) and LRP (second interval) – obtained in relation to the hand of the response at C3/4 electrodes pair – are shown for the compatible position (CP) (solid line), incompatible position (IP) (dashed line) and neutral position (NP) (dotted line). The N2cc/LRP peak amplitude was smaller in the IP than in the CP and NP conditions because the correct response preparation was present in the CP and NP conditions, but was delayed in the IP condition — as shown by the longer LRP peak latency in the second interval in IP condition (Fig. 3.1). The N2pc (obtained in relation to the hemifield of stimulus presentation at P7/8 electrodes) revealed a lack of any differences between the CP (solid line) and the IP (dashed line) conditions (Fig. 3.2); The HEOG for CP (solid line), IP (dashed line) and NP (dotted line) conditions did not reveal any differences between the three conditions as regards ocular movements to the stimulus position (Fig. 3.3).

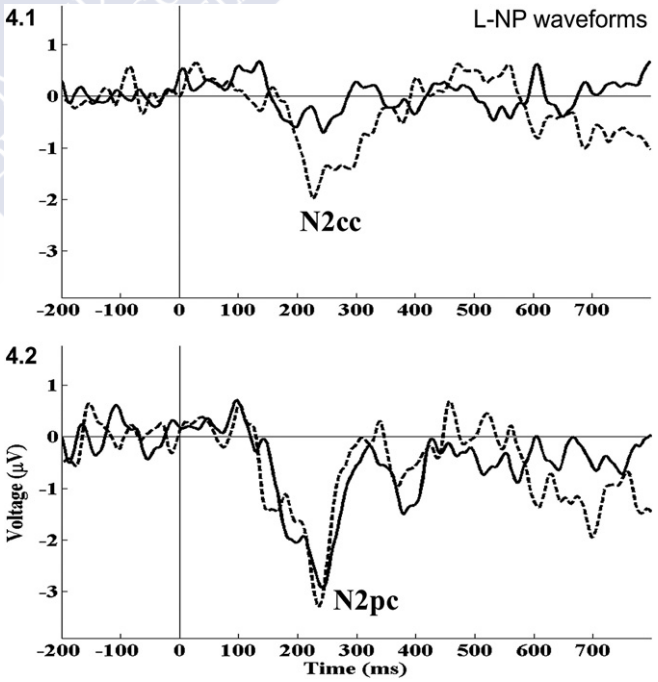

Fig. 4. N2cc (top) and N2pc (bottom) waveforms are shown after removal of the motor activity through lateralized minus neutral position (L − NP) subtractions for the compatible position (CP) (solid line) and the incompatible position (IP) (dashed line) at the C3/4 and P7/8 electrodes. The amplitude of the N2cc component was larger in the IP than in the CP condition. This indicates that greater inhibitory control of the stimulus position was required in the IP, in order to prevent cross-talk between the direction of spatial attention and the manual response activation (Fig. 4.1). There were no differences in the N2pc component between CP and IP conditions, as the interference locus in the Simon effect is not present in the visuospatial processing of the relevant stimulus. Evidence of functional dissociation between both N2cc and N2pc components was obtained since they were differently affected by the experimental manipulation (Fig. 4.2).

−1.504, p = 0.155) ($IP_{\text{right-hand movements}} - NP_{\text{right-hand movements}}$ at C3 (t (14) = 0.891, p = 0.388)). The one sample t-tests revealed significant differences from zero at the electrodes contralateral to the position of the stimuli ($IP_{\text{left-hand movements}} - NP_{\text{left-hand movements}}$ at C3 (t (14) = −4.216, p = 0.001); $IP_{\text{right-hand movements}} - NP_{\text{right-hand movements}}$ at C4 (t (14) = −1.922, p = 0.075)).

3.3. eLORETA

The brain regions in which the SnPM log-F-ratio statistic for paired groups was significant are shown, along with the MNI coordinates, in Table 2. The regions in which the brain activity differed between conditions are shown in Fig. 5.

In the 150–200 ms interval, the activity was greater in the CP than in NP condition (log-F-ratio = 1.3, p = 0.034), and in IP than in NP condition (log-F-ratio = -1.0, p = 0.006) in premotor areas.

In the 200–250 ms interval, the activity was greater in the CP than in NP condition, mainly in Brodmann areas 5 and 7 (log-F-ratio = 1.1, p = 0.018) (see Table 2 and Fig. 5).

4. Discussion

A Simon effect was observed in the present study (a longer Reaction Time, RT, in the incompatible position (IP) than in the compatible position (CP)). Consistent with the Simon effect, the LRP peak latency was longer in the IP than in the CP condition. The N2cc amplitude of the lateralized minus neutral position (L − NP) waveforms was larger in the IP than in the CP condition. This indicated that more resources were engaged in monitoring the selection of the response in IP than in CP. The eLORETA analysis revealed greater premotor activity in CP and IP (where N2cc activity was expected to appear) than in NP, in a temporal window between 150 and 200 ms. Otherwise there were no differences in N2pc according to the experimental manipulation, providing new evidence of functional dissociation between N2pc and N2cc components.

The behavioural results revealed a Simon effect due to stimulus–response interference in the IP condition, manifested by a longer reaction time (RT) and a higher percentage of errors (PE) in the IP condition than in the CP and in the NP conditions. These results are consistent with those of previous studies (see Lu and Proctor, 1995). There was no facilitation effect since there were no significant differences between the NP and CP conditions in the RT, PE, DA and LRP measures. The absence of differences between CP and NP in the different measures also indicates that the different eccentricity of both stimuli did not affect the performance. Moreover, the HEOG showed an absence of any differences between the three conditions of the task as regards ocular movements to the stimulus position, probably because of the short time of stimuli presentation, as suggested by Abrahamse and Van der Lubbe (2008).

With respect to electrophysiological measures, a longer LRP peak latency was observed in IP than in CP condition, which is consistent with the RT and with the results of previous studies (Praamstra and Plat, 2001). Although the onset of the correct response cannot be measured in horizontal arrangements due to the N2cc/LRP overlap, studies that used vertical arrangements of stimuli and responses (de Jong et al., 1994; Stürmer et al., 2002; Valle-Inclán, 1996, Experiment 3) established that the interference occurred during the response selection. However, as explained below, the horizontal arrangement of the stimuli enabled better comprehension of the effects of stimulus position on the visuospatial processing of the relevant stimulus and

Table 2
Cortical regions significantly activated (by means of eLORETA) in the paired comparisons between conditions. Left panel: NP vs. IP (150–200 ms); middle panel: CP vs. NP (150–200 ms); right panel: CP vs. NP (200–250 ms). BA: Brodmann area; MNI: Montreal Neurological Institute.

Anatomical region (BA) NP vs. IP (150–200 ms)	MNI coordinates			Anatomical region (BA) CP vs. NP (150–200 ms)	MNI coordinates			Anatomical region (BA) CP vs. NP (200–250 ms)	MNI coordinates		
	X	Y	Z		X	Y	Z		X	Y	Z
Precentral gyrus (6)	−15	−20	70	Medial frontal gyrus (6)	−5	−30	70	Paracentral lobule (5)	−5	−50	65
Superior frontal gyrus (6)	−20	−15	70	Paracentral lobule (4)	5	−40	70	Postcentral lobule (2)	−30	−40	70
Superior frontal gyrus (6)	−15	−15	70	Paracentral lobule (4)	−5	−35	70	Precuneus (7)	−5	−50	60
Precentral gyrus (6)	−10	−20	70	Paracentral lobule (4)	5	−35	70	Postcentral gyrus (5)	−10	−50	65
Precentral gyrus (6)	−20	−20	70	Paracentral lobule (4)	−5	−40	70	Postcentral gyrus (2)	−30	−40	65
Medial frontal gyrus (6)	−5	−20	70	Postcentral lobule (5)	5	−45	70	Postcentral gyrus (5)	−5	−50	70
Medial frontal gyrus (6)	−10	−15	70	Postcentral gyrus (5)	−5	−25	70	Precuneus (7)	−5	−55	65
Middle frontal gyrus (6)	−20	−15	65	Medial frontal gyrus (6)	5	−30	70	Precuneus (7)	−10	−50	60
Superior frontal gyrus (6)	−20	−10	70	Medial frontal gyrus (6)	0	−35	65	Postcentral gyrus (7)	−5	−55	70
Medial frontal gyrus (6)	0	−25	65	Postcentral lobule (5)	−5	−45	70	Postcentral gyrus (5)	−10	−50	70
Medial frontal gyrus (6)	0	−25	65	Medial frontal gyrus (6)	0	−30	65	Postcentral gyrus (7)	−10	−55	65
Medial frontal gyrus (6)	−5	−25	70	Paracentral lobule (5)	5	−35	65	Postcentral gyrus (7)	−10	−55	70
Medial frontal gyrus (6)	5	−25	60	Postcentral gyrus (5)	−5	−50	70	Precuneus (7)	−5	−55	60
Precentral frontal gyrus (6)	−25	−15	70	Postcentral gyrus (5)	10	−35	70	Postcentral gyrus (5)	−30	−45	70
Medial frontal gyrus (6)	5	−25	65	Medial frontal gyrus (6)	5	−30	65	Postcentral gyrus (5)	−25	−45	70
Medial frontal gyrus (6)	−5	−15	70	Medial frontal gyrus (6)	−5	−30	65	Postcentral gyrus (2)	−25	−40	65
Medial frontal gyrus (6)	−5	−20	60	Paracentral lobule (5)	0	−40	65	Postcentral gyrus (7)	−15	−55	70
Superior frontal gyrus (6)	−15	−10	70	Paracentral lobule (5)	5	−40	65	Postcentral gyrus (2)	−25	−40	70
Medial frontal gyrus (6)	0	−30	60	Precentral gyrus (4)	−15	−30	70	Precuneus (7)	−5	−50	55
Medial frontal gyrus (6)	5	−30	60	Postcentral gyrus (4)	10	−35	70	Postcentral gyrus (5)	−20	−50	70
Medial frontal gyrus (6)	0	−30	65	Precentral gyrus (4)	10	−30	70	Precuneus (7)	−5	−55	55
Medial frontal gyrus (6)	-5	−30	65					Precuneus (7)	0	−55	65
Medial frontal gyrus (6)	5	−20	65					Postcentral gyrus (5)	−25	−45	65
								Sub-gyrus (40)	−25	−40	60
								Postcentral gyrus (40)	−30	−40	60
								Precuneus (7)	−10	−50	55
								Postcentral gyrus (7)	−15	−55	65
								Precuneus (7)	−10	−55	55
								Precuneus (7)	−15	−50	60
								Superior parietal (5)	−20	−45	65
								Postcentral gyrus (5)	5	−50	70
								Precuneus (7)	0	−55	60
								Postcentral gyrus (5)	−5	−45	65
								Superior parietal (7)	−20	−50	65
								Postcentral gyrus (7)	−10	−60	70

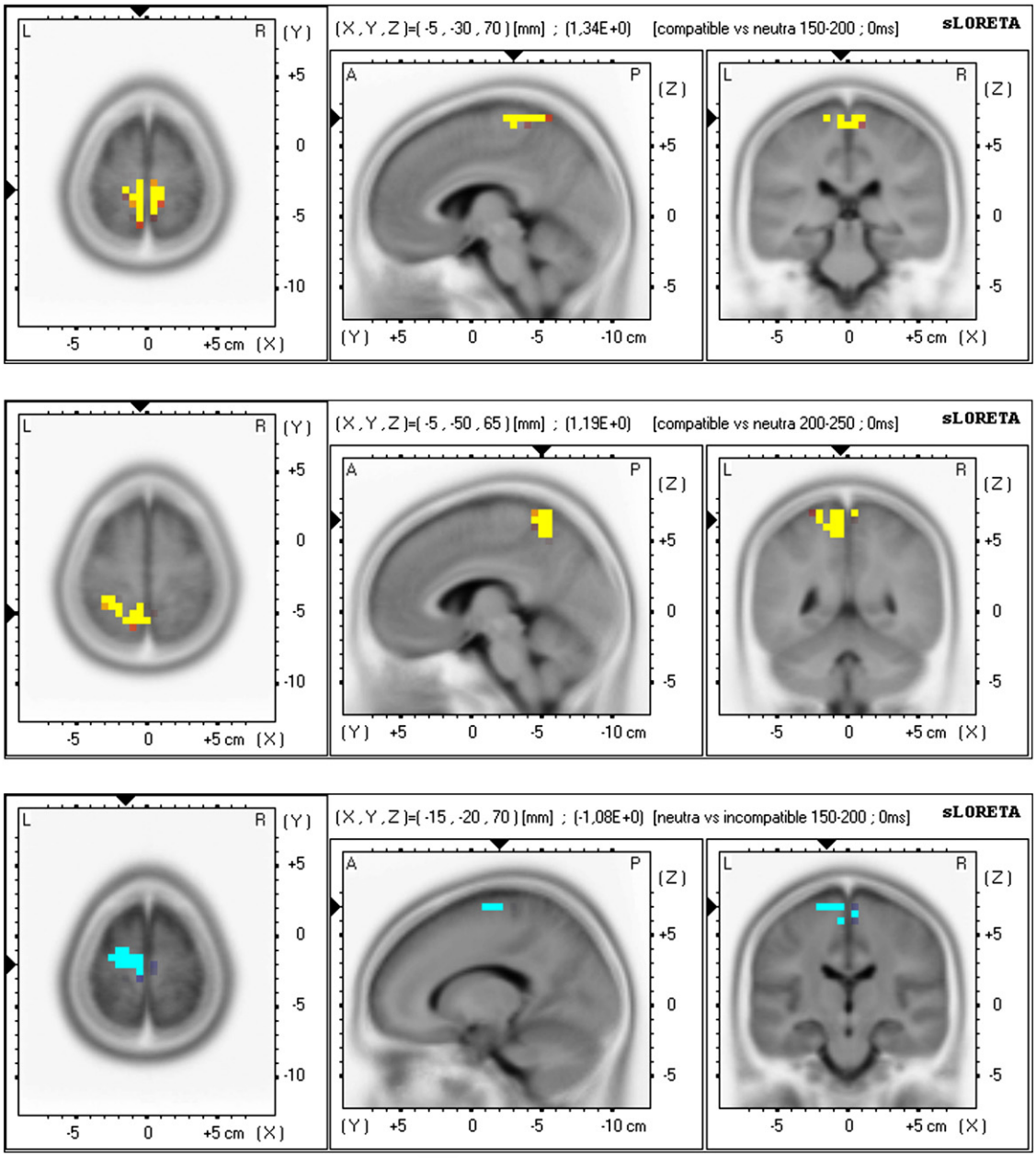

Fig. 5. eLORETA tomographies with the regions that showed significantly higher activation in the comparisons between CP and NP, and between NP and IP. In the comparison between CP and NP, greater activation for CP than for NP is indicated in yellow and red, between 150–200 ms (top) and 200–250 ms (middle). In the comparison between NP and IP (bottom), the lower activation in the 150–200 ms window for NP than for IP is indicated in blue. Greater activation in premotor regions was observed in both the CP and IP conditions relative to the NP condition in the 150–200 ms interval.

the cognitive control used to monitor the tendency of response based on the stimulus position, i.e. the processes related to N2pc and N2cc.

In the present study, the motor activity was removed through the L − NP waveforms with the purpose of studying how N2cc and N2pc components are modulated on the basis of whether the stimulus position is compatible or incompatible with the response. In these L − NP waveforms, N2pc did not present any modulation related to the experimental manipulation. This indicated that the Simon effect does not occur in the visuospatial processing of the relevant stimulus (Praamstra and Oostenveld, 2003; Van der Lubbe and Verleger, 2002). In relation with these findings, eLORETA analysis revealed greater activity in Brodmann areas 5 and 7, within the 200–250 ms interval, in CP than in NP. Although there were no such differences in activation between IP and NP, they may be related to the N2pc component, which is present in the CP but absent in the NP condition (Luck and Hillyard, 1994; Woodman and Luck, 1999, 2003).

The N2cc amplitude was larger in IP-NP than in CP-NP, which is consistent with the higher activity associated with the cognitive control of the response in the IP than in the CP condition. Nonetheless, the *t*-test revealed that the N2cc amplitude was significantly larger than zero in the CP condition (Fig. 4.1). In addition, the eLORETA analysis revealed greater activity in premotor regions in CP and IP than in the NP condition between 150 and 200 ms. This activity appears to be related to the N2cc component since it was observed in the spatially lateralized conditions (CP and IP) in which N2cc was expected to appear. Although the results should be considered with caution in light of the low spatial resolution of the eLORETA, the activity occurred in a region consistent with the sources of N2cc, the

premotor cortex (see Praamstra and Oostenveld, 2003), and within the temporal window in which N2cc was expected to appear (Leuthold and Schröter, 2006), although it was more consistent with the onset of L − NP than with the L − NP peak.

Some limitations inherent to the subtraction procedures have been pointed out (see Van Boxtel, 2004). Specifically, the new waveforms obtained through subtraction procedures are usually derived from differences in latency or amplitude from the constituent waveforms. Thus, the L − NP waveforms may have resulted from differences in motor activity not subtracted from CP and IP (with respect to the NP condition), thus leading to confusing interpretations. However, there were no differences between CP and NP in behavioural (RT, PE and DA) and electrophysiological parameters (LRP peak latency) in relation to motor activity. This suggests that motor activity was removed through the CP-NP subtraction. The L − NP waveform observed in the CP condition and the differences revealed by eLORETA in the comparison between CP and NP may therefore be due to the N2cc, which is present in the CP but not in the NP condition where the stimuli are not spatially lateralized.

With respect to possible residual motor activity in the IP − NP subtraction, differences in RT were observed throughout the distribution of RTs. Also, the greater positivity for IP than NP mainly occurred between 200 and 300 ms (see Fig. 3.1). This positivity may be due to the preparation of the incorrect response and/or subsequent delay in preparing the correct movement in IP with respect to NP. If so, it would contaminate the L − NP waveform in the IP condition because of residual motor activity still present after subtraction. To study this possibility, t-tests were applied to the first set of subtractions (Fig. 2.1) for the average amplitude between 220 and 270 ms (i.e. when a larger N2cc was observed in the L − NP waveform) at electrodes C3 and C4. The t-tests revealed that the IP − NP subtraction did not result in a significant waveform at central electrodes contralateral to the hand of the response. On the contrary, after subtraction, significant negativity was observed at electrodes contralateral to the hemifield of presentation of the stimulus. Thus, the L − NP waveform in the IP condition was the sum of the corresponding negativities contralateral to the hemifield of presentation of the stimuli.

It could be argued that preparation of the incorrect response in the IP is still present in the L − NP waveform, since it would be absent in NP. In fact, the positive wave observed, through LRP derivation, in the IP condition (see Fig. 3.1) is very similar to the wave associated with preparation of the incorrect response in vertical Simon tasks (Valle-Inclán, 1996, Experiment 3). However, such a positive wave has been related to the N2cc component in horizontal Simon tasks (Praamstra, 2006). Praamstra (2006) compared one horizontal Simon task in which the participants responded to the stimulus as soon as it was presented on the screen, with another horizontal Simon task in which the response was delayed until the appearance of a signal. As the functional role of N2cc is to prevent cross-talk between the direction of the spatial attention and the manual response preparation (Praamstra and Oostenveld, 2003), no underlying N2cc-related activity was required in the second task since an attentional shift to the stimulus position and manual response preparation occurred at different times. Although the effect of interference was similar in both tasks, the positive wave was only present in the incompatible condition of the first task. This showed that such positivity was related to N2cc activity and not to preparation of the incorrect response, as also supported by data from dipole source models (Praamstra, 2006).

The lateralization of the premotor activity to the left hemispheric revealed by eLORETA is consistent with differences between both conditions in the N2cc component. Previous studies have suggested that the left hemisphere makes a greater contribution to the N2cc than the right hemisphere (Praamstra and Oostenveld, 2003). This is also consistent with the lateralization of the dPM during monitoring of the response selection: left hemisphere lesions have a disruptive effect on the ability of patients to select between movements according to arbitrary rules (Rushworth et al., 1998). In addition, transcranial magnetic stimulation (TMS) of the left PMd disrupts the selection of movements that will be made by either hand (Johansen-Berg et al., 2002; Schluter et al., 1998).

In accordance with the activity observed in the premotor cortex, other studies using techniques with higher spatial resolution, e.g. PET and fMRI (Corbetta et al., 1993; Gitelman et al., 1999; Rosen et al., 1999), have shown that the premotor cortex is activated by attentional changes. Furthermore, fMRI studies specifically focused on the Simon effect have detected activation in the dorsal premotor cortex (Petersen et al., 2002; Wittfoth et al., 2006) and in the supplementary motor area (Liu et al., 2004; Wittfoth et al., 2006), which the authors attributed to resolution of the conflict.

The evidence from L − NP waveforms suggests that N2cc activity is greater in the IP than in the CP condition. These results therefore support the suggestion of N2cc as a mechanism involved in monitoring the response selection (Praamstra and Oostenveld, 2003). Greater effort would be necessary in the IP condition to select the appropriate response since it does not coincide with the spatially compatible response. The increased effort would be related to greater activity associated with N2cc. Stürmer and Leuthold (2003) proposed an ancillary monitoring mechanism (AMM) in Simon tasks, which would be responsible for monitoring the response selection and selectively suppressing output of the unconditional route whereby location-based signals are prevented from accessing the motor system. The present results are consistent with the suggestion of Leuthold and Schröter (2006) that the N2cc component represents such a cognitive control mechanism.

Moreover, the present results obtained by means of the L − NP subtractions provide further support for the functional dissociation between N2cc and N2pc (Praamstra, 2006; Praamstra and Oostenveld, 2003), as differences in amplitude between conditions were found for N2cc but not for N2pc. This functional dissociation is consistent with the findings of some studies that identified different foci of activity associated with N2pc and N2cc (Oostenveld et al., 2001; Praamstra and Oostenveld, 2003; Praamstra and Plat, 2001).

The present study used a horizontal arrangement of stimuli and responses whereby the measure of the covert response activation (LRP onset) was sacrificed in benefit of the study of N2pc and N2cc components, since the N2cc plays an important role in spatial stimulus–response compatibility tasks that is worthy of further research, as concluded in the review by Leuthold (2011). As far as we are concerned, the present results showed for the first time that N2cc activity was higher when the stimulus position was spatially incompatible than when it was spatially compatible with the required response. The N2cc component may therefore be a useful tool for evaluating populations in which deficits in spatial response inhibition are expected to occur.

5. Conclusions

In the present study, the motor activity was eliminated through L − NP subtractions, which revealed a larger N2cc amplitude in IP than in CP, in accordance with the greater effort required to monitor selection of the correct response in the IP condition. Additional information about N2cc was provided by eLORETA analysis, which revealed greater premotor activity, between 150 and 200 ms, in IP and CP than in NP. The functional dissociation between N2pc and N2cc components was indicated by the fact that N2cc, but not N2pc, was differentially affected by the experimental condition.

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2.2 Study 2 (Estudio 2)

Cespón, J., Galdo-Álvarez, S., & Díaz, F. (2013). N2pc is modulated by stimulus-stimulus, but not by stimulus-response incompatibilities. *Biological Psychology 93*, 75-80.

Estudios sobre N2pc en tareas tipo Simon han revelado resultados inconsistentes. En concreto, sólo se observó una modulación sobre la amplitud de N2pc cuando un solapamiento estímulo-estímulo (E-E) covariaba con el solapamiento estímulo-respuesta (E-R). El presente estudio pretendía establecer si N2pc era modulada por el solapamiento E-R o por el solapamiento E-E. En consecuencia, en el presente estudio diseñamos una tarea Simon en la que se instruía a los participantes a responder al color del estímulo (una flecha roja o azul), el cual tenía dos dimensiones irrelevantes (posición y dirección de la flecha). La combinación de ambas dimensiones irrelevantes daba lugar a las siguientes condiciones experimentales: dirección compatible - posición compatible (CDCP), dirección incompatible - posición compatible (IDCP), dirección compatible - posición incompatible (CDIP), dirección incompatible - posición incompatible (IDIP). En las condiciones IDCP y CDIP, las dos dimensiones irrelevantes proporcionaban información espacial contradictoria (incompatibilidad E-E, es decir, la dirección apuntaba hacia el lado contrario respecto a la ubicación de la flecha) mientras que en CDCP e IDIP las dos dimensiones irrelevantes proporcionaban la misma información espacial (compatibilidad E-E). Los resultados mostraron una menor amplitud de N2pc en IDCP y CDIP que en CDCP e IDIP. Este resultado sugirió que la N2pc estaba modulada por el solapamiento E-E y no por el solapamiento E-R, ya que la amplitud de N2pc fue menor en las condiciones donde estaba presente la incompatibilidad E-E.

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N2pc is modulated by stimulus–stimulus, but not by stimulus–response incompatibilities

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ABSTRACT

Studies of the N2pc in Simon-type tasks have revealed inconsistent results. That is, N2pc was only modulated when a stimulus–stimulus (S-S) overlap covaries with the stimulus–response (S-R) overlap. The present study aimed to establish whether N2pc is modulated by the S-R or by the S-S overlap. Therefore, we designed a Simon task requiring response to a colour stimulus (an arrow) with two irrelevant dimensions (position and direction). The following conditions were thus generated: compatible direction–compatible position (CDCP); incompatible direction–compatible position (IDCP); compatible direction–incompatible position (CDIP); and incompatible direction–incompatible position (IDIP). In IDCP and CDIP, both irrelevant dimensions conveyed contradictory spatial information (S-S incompatibility), while compatibility between both irrelevant dimensions occurred in CDCP and IDIP (the direction indicated was compatible with stimulus position). The N2pc amplitude was smaller in IDCP and CDIP than in CDCP and IDIP, what suggests that N2pc was modulated by S-S incompatibility and not by S-R incompatibilities.

1. Introduction

The Simon task is a type 3 stimulus–response compatibility task (SRC) (for a classification of SRC types, see Zhang et al., 1999) in which the participants respond to a feature (e.g. colour, shape, etc.) of spatially lateralized stimuli by pressing one of two buttons. The response buttons are also lateralized in the same spatial arrangement as the stimuli, with the position of the stimulus irrelevant to the task. In those cases in which the required response is on the opposite side to the stimulus (incompatible condition), an interference effect known as the Simon effect is produced (for reviews, see Leuthold, 2011; Lu and Proctor, 1995; Simon, 1990). The interference is manifested by a longer reaction time (RT) in the incompatible condition than in the compatible condition.

The temporal locus of the interference in SRC tasks, particularly in the Simon task, is of great interest. The high temporal resolution of the event-related potentials (ERP) allows this locus to be established. The lateralized readiness potential (LRP) is an ERP component that is widely used to investigate the temporal locus of the Simon effect (see Gratton et al., 1988). Analysis of the LRP has revealed that the temporal locus of the Simon effect occurs at the response selection stage (De Jong et al., 1994; Stürmer et al., 2002; Valle-Inclán, 1996); interference has also been reported at the response execution stage (Ansorge and Wühr, 2004; Vallesi et al., 2005). Similar loci of interference have been observed in another SRC task, in which the direction indicated by a central arrow was considered an irrelevant dimension when the participants were responding to the colour of the arrow (Masaki et al., 2000).

It is possible that visuospatial processing of the stimulus plays an important role in the Simon task because the stimuli are spatially lateralized. The N2pc (negativity posterior contralateral) is an ERP component related to the visuospatial processing of the stimulus (Luck and Hillyard, 1994; Woodman and Luck, 1999, 2003). The sources of N2pc have been localized in extraestriate visual areas (Hopf et al., 2000; Luck et al., 1997), and the component has been observed at 200–250 ms, as enhanced negativity at posterior electrodes contralateral to the hemifield in which the stimuli were presented (Eimer, 1996). The importance of studying the N2pc component in this type of task was highlighted in a recent review of electrophysiological studies of the Simon effect (Leuthold, 2011), although studies addressing modulation of the N2pc by the Simon effect are scarce and show inconsistent results.

In some studies using Simon tasks, N2pc modulations were not observed in relation to the experimental condition (Cespón et al., 2012; Praamstra, 2006; Praamstra and Oostenveld, 2003; Van der Lubbe and Verleger, 2002). However, Valle-Inclán (1996, Exp. 2) observed a larger N2pc amplitude in the incompatible condition than in the compatible condition. This suggested that, in addition

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to the interference observed in response-related processes, interference took place at stimulus processing stages in the Simon effect.

The discrepancies in the results regarding N2pc modulation may have been caused by a stimulus–stimulus overlap (S-S) in the Simon task used by Valle-Inclán (1996), which was not present in the tasks used in the other studies mentioned. In the study carried out by Valle-Inclán (1996), the participants responded to the direction indicated by a lateralized arrow and ignored the stimulus position. Thus, in addition to the overlap between the irrelevant dimension and the response, there was also an overlap between the relevant dimension (the direction of the arrow pointing to the right or to the left) and the irrelevant dimension of the stimulus (the position of the arrow, which was placed on the right or on the left of the screen). However, in the previously mentioned studies, the relevant dimension, which was a letter (Praamstra and Oostenveld, 2003; Van der Lubbe and Verleger, 2002), a coloured arrow pointing upwards (Cespón et al., 2012), or a square containing horizontal bars (Praamstra, 2006), did not overlap with the irrelevant dimension (stimulus position) (e.g. a specific letter is not compatible or incompatible with a right or left side position, unlike arrows pointing to the right or to the left. For a review on the dimensional overlap, see Zhang et al., 1999).

It is known that the stimulus position and the direction pointed by an arrow may orient spatial attention (Klein, 2004; Klein and Ivanoff, 2011). Consequently, when the arrow is in the opposite hemifield with respect to where it is pointing, conflicting spatial information may be produced, causing a decline in the allocation of spatial attention to the stimulus position, which would be reflected by changes in the N2pc.

In the type of task used by Valle-Inclán (1996), it is not possible to dissociate S-S and S-R effects since the S-S incompatibility is always accompanied by S-R incompatibility and the S-S compatibility is always accompanied by the S-R compatibility (Juncos-Rabadán et al., 2008). Therefore, the N2pc modulation could not be attributed to S-R incompatibility (Simon effect) or to S-S incompatibility. However, Valle-Inclán (1996) observed a larger N2pc amplitude in the incompatible condition than in the compatible condition and interpreted this as interference at a perceptual processing stage. Although some studies have related increased N2pc amplitude to greater difficulty in suppressing the non-target stimulus (Luck et al., 1997), the N2pc was related to target processing (Eimer, 1996) in tasks in which a single contralateral non-target is presented. Furthermore, recent evidence supports the idea that the N2pc amplitude is smaller when the allocation of attentional resources to the target is less efficient (Hilimire et al., 2009, 2010; Telling et al., 2009).

The aim of the present study was to determine whether the S-S incompatibility affected allocation of the visuospatial attention to the target stimulus. For this purpose, it was necessary to dissociate S-S and S-R incompatibilities, and therefore we designed a task in which the participants were asked to respond to the colour of an arrow, but to ignore the position and the direction pointed by the arrow. As a result of the combination of both irrelevant dimensions, the task included four conditions (Fig. 1a): compatible direction/compatible position (CDCP), in which S-R compatibility based on the stimulus position was accompanied by S-S compatibility (compatible position S-R/compatible S-S); incompatible direction/compatible position (IDCP), in which S-R compatibility based on the stimulus position was accompanied by S-S incompatibility (compatible position S-R/incompatible S-S); compatible direction/incompatible position (CDIP), in which S-R incompatibility based on the stimulus position was accompanied by S-S incompatibility (incompatible position S-R/incompatible S-S); and incompatible direction/incompatible position (IDIP), in which S-R incompatibility based on the stimulus position was accompanied by S-S compatibility (incompatible position S-R/compatible S-S) (the task stimuli are illustrated in Fig. 1a and a diagram of the experimental design is shown in Fig. 1b).

According to recent views of N2pc modulations, a smaller N2pc amplitude is expected when the difficulty in allocating attentional resources to the target stimulus increases. Three alternative hypotheses were considered in the present study. Firstly, if the S-S incompatibility interferes with the allocation of attention to the target stimulus, then a smaller N2pc amplitude would be expected in incompatible S-S (IDCP and CDIP, in which incompatibility between the position and the direction was present, i.e. the arrow was placed in the opposite hemifield with respect to where it was pointing) than in compatible S-S (CDCP and IDIP conditions) (Hypothesis 1, see Fig. 1c). Secondly, if the Simon effect causes a decline in visuospatial attention to the target stimulus, then a smaller N2pc amplitude would be expected in the incompatible position S-R (CDIP and IDIP, in which the position was incompatible with the response) than in the compatible position S-R (CDCP and IDCP conditions) (Hypothesis 2, see Fig. 1d). A third possibility is that the direction of the arrow modulates the N2pc component. In this case, a smaller N2pc amplitude would be expected in incompatible direction S-R (IDCP and IDIP, in which the direction was incompatible with the response) than in the compatible direction S-R (CDCP and CDIP conditions) (Hypothesis 3, see Fig. 1e).

2. Methods

2.1. Participants

Twenty-one participants (14 women) between 19 and 28 years of age agreed to take part in the study and were paid for their participation. The study received prior approval by the local ethical review board. Twenty participants were right-handed and one was ambidextrous, as evaluated by the Edinburgh Handedness Inventory (Oldfield, 1971). All participants had normal or corrected to normal vision and none had any history of neurological or psychiatric disorders.

2.2. Stimuli and procedure

A red or blue arrow pointing either left or right was displayed on a screen against a black background. The screen was placed 100 cm in front of the participants. The arrow stimuli subtended 2.87° horizontally and 1.72° vertically in the visual field and were presented in parafoveal region (the internal edge was 2.29° and the external edge 5.16° of visual angle with respect to a central cross: see Bargh and Chartrand, 2000). A geometric figure of similar morphology (see Fig. 1a) and eccentricity was presented in the opposite hemifield with respect to the position of the arrow. Both stimuli were presented for 125 ms (2000 ms inter-trial intervals).

The participants were instructed to direct their gaze to the central cross throughout the task and to respond to the colour of the arrow by pressing one of two horizontally arranged buttons. The following experimental conditions were generated: compatible direction–compatible position (CDCP), incompatible direction–compatible position (IDCP), compatible direction–incompatible position (CDIP), and incompatible direction–incompatible position (IDIP) (see Fig. 1a). After a practice block of 24 trials, 320 trials (80 per condition) were presented in two blocks (90 s inter-block interval). The response button assigned to each colour of the arrow was counterbalanced among participants, who were instructed to respond as quickly and accurately as possible.

2.3. EEG recordings

Forty-nine active electrodes were used for the EEG recordings, in accordance with the 10–10 International System: AFz, AF3, AF4, AF7, AF8, Fz, F3, F4, F5, F6, F7, F8, FCz, FC1, FC2, FC3, FC4, FT7, FT8, FT9, FT10, Cz, C1, C2, C3, C4, C5, C6, T7, T8, CPz, CP3, CP4, TP7, TP8, TP9, TP10, Pz, P3, P4, P7, P8, P9, P10, PO7, PO8, Oz, O1 and O2. The EEG signal was passed through a 0.01–100 Hz analogue bandpass filter and was sampled at 500 Hz. The reference electrode was placed on the tip of the nose and the ground electrode at Fpz. Recordings of vertical ocular movement (VEOG) and horizontal ocular movement (HEOG) were obtained with two electrodes located supra- and infraorbitally to the right eye and two electrodes at the external canthus of each eye, respectively. Impedances were maintained below 10 kΩ. After signal storage, ocular artefacts were corrected offline by use of the algorithm proposed by Gratton et al. (1983). The signal was filtered at 0.01–30 Hz digital band-pass. Epochs exceeding ±100 μV were automatically rejected, and all remaining epochs were individually inspected to identify those still displaying artefacts; these epochs were also excluded from subsequent averaging. Epochs were then corrected to the mean voltage of the 200-ms pre-stimulus recording period (baseline).

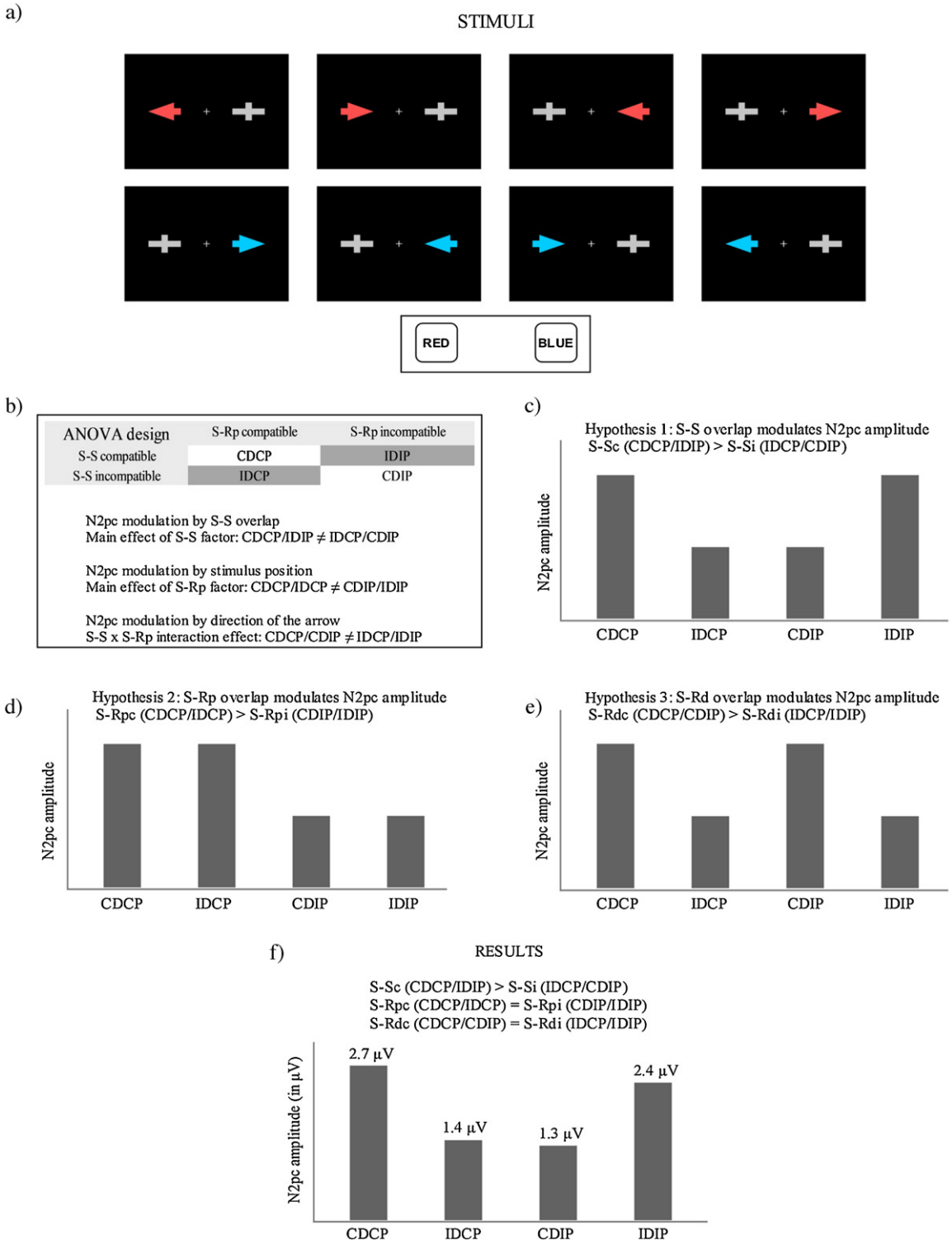

Fig. 1. (a) Diagram showing the task and stimuli presented. Participants were instructed to respond by pressing the left button with their left hand when a red arrow appeared and the right button with their right hand when a blue arrow appeared, so that the conditions presented (from left to the right columns) were respectively: compatible direction/compatible position (CDCP); incompatible direction/compatible position (IDCP); compatible direction/incompatible position (CDIP); and incompatible direction/incompatible position (IDIP). The response buttons were counterbalanced among participants. (b) ANOVA design. The main factors were stimulus–stimulus (S-S) and stimulus–response compatibility based on the position (S-Rp). Effects of direction of the arrow (S-Rd) would be revealed by S-S × S-R interaction effects (note that the white diagonal line = compatible direction, and the grey diagonal line = incompatible direction). (c) Pattern of results expected if stimulus–stimulus (S-S) modulates N2pc amplitude. (d) Pattern of results expected if stimulus–response based on the stimulus position (S-Rp) modulates N2pc amplitude. (e) Pattern of results expected if stimulus–response based on the direction pointed by the arrow (S-Rd) modulates N2pc amplitude. (f) Results of N2pc amplitude showing that S-S overlaps (and not S-R overlaps) modulated the amplitude of N2pc.

Table 1
Values in each condition (compatible direction and compatible position, CDCP; incompatible direction and compatible position, IDCP; compatible direction and incompatible position, CDIP; incompatible direction and incompatible position, IDIP) for reaction time (RT, in ms), percentage of errors (PE), averaged amplitude (in μV) of N2pc between 200 and 270 ms; peak latency (in ms) of N2pc; and averaged amplitude (in μV) of N2cc between 200 and 270 ms.

Condition	CDCP	IDCP	CDIP	IDIP
Reaction time	404 (39)	416 (42)	450 (41)	455 (44)
Percentage of errors	3.1 (3.4)	3.5 (3.1)	8.7 (7.2)	9.9 (4.6)
N2pc peak latency	237 (20)	230 (26)	236 (26)	241 (17)
N2pc amplitude	−2.7 (1.9)	−1.4 (1.8)	−1.3 (2.3)	−2.4 (1.8)
N2cc amplitude	−2.2 (1.3)	−1.6 (0.8)	−0.6 (0.9)	−0.4 (1.3)

2.4. Data analysis

Trials with incorrect responses or RTs outside the 100–1000 ms range were excluded from the analysis. The RTs and the percentage of errors (PE) were calculated.

Epochs were established between −200 and 800 ms associated with presentation of the stimulus. Following previous studies (e.g. Kiss et al., 2008), in the present study a two-step procedure was used to remove epochs with horizontal ocular artefacts. Firstly, trials with large horizontal eye movements (larger than ±30 μV) were removed. Secondly, averaged HEOG waveforms showing residual eye movements (HEOG activity exceeding ±3 μV) were eliminated. Three participants were excluded from further analyses because they displayed residual horizontal ocular movements in all conditions. The number of averaged epochs in each experimental condition was as follows: CDCP (61 averaged epochs/19 excluded epochs), IDCP (56 averaged epochs/24 excluded epochs), CDIP (57 averaged epochs/23 excluded epochs), and IDIP (58 averaged epochs/22 excluded epochs). The N2pc component was determined in relation to the hemifield of the target presentation, as follows: [PO8–PO7 (left hemifield) + PO7–PO8 (right hemifield)]/2 (see Luck and Hillyard, 1994). The latency of N2pc was measured as the largest negative peak between 200 and 270 ms, determined by inspection of the grand averages. Amplitudes of N2pc were calculated as the mean value between 200 and 270 ms (i.e. the usual procedure for measuring N2pc amplitude, e.g. Woodman and Luck, 1999).

Incompatibility from the position modulates motor (Valle-Inclán, 1996) and negativity central contralateral (N2cc) (Cespón et al., 2012) components, and incompatibility from the direction also modulates motor activity (Masaki et al., 2000). As these modulations and those of the N2pc amplitude occur in a similar temporal window, the procedure for obtaining N2pc was applied at central electrodes, [C4–C3 (left hemifield) + C3–C4 (right hemifield)]/2, to test for possible effects of volume conduction from central regions on the N2pc. The N2cc amplitudes were calculated as the mean value between 200 and 270 ms (note that the wave recorded at central electrodes is labelled as N2cc, although it is actually constituted by overlapping between N2cc and motor activity (LRP), Praamstra, 2007).

2.5. Statistical analysis

The RT, percentage of errors (PE), and ERP data were analysed by ANOVA, with the stimulus–stimulus compatibility (S-S) (two levels: compatible and incompatible) and the stimulus–response compatibility based on the stimulus position (S-R) (two levels: compatible and incompatible) as within-subject factors. Therefore, S-S or S-R effects due to the stimulus position would be revealed by a main effect, while S-R effects due to the direction indicated by the arrow would be revealed by an S-S × S-R interaction effect (see Fig. 1b, showing a diagram of the design).

Repeated measures ANOVAs were used to determine whether there were any differences in the RTs, the PE, the N2pc peak latency and averaged amplitude, and the N2cc averaged amplitude in relation to the experimental conditions. Two within-subject factors were considered: S-S (two levels: compatible and incompatible) and S-R (two levels: compatible and incompatible). When the ANOVAs revealed significant effects due to the factors and their interactions, post hoc paired multiple comparisons of the mean values were carried out (with Bonferroni correction).

3. Results

3.1. Behavioural measures

For the RT (see Table 1), the repeated measures ANOVA (S-S × S-R) revealed a significant effect of the S-R factor (F (1, 17) = 143.4, $p < 0.001$, $\eta_\rho^2 = 0.894$), as the RTs were shorter in compatible S-R trials (CDCP/IDCP) than in incompatible S-R trials (CDIP/IDIP) ($p < 0.001$, $\eta_\rho^2 = 0.894$). An S-R × S-S interaction effect was observed (F (1, 17) = 11.8, $p = 0.003$, $\eta_\rho^2 = 0.411$); specifically, when the S-R was compatible, the RT was longer when the S-S was also incompatible ($p = 0.009$, $\eta_\rho^2 = 0.342$) (i.e. the RT was longer in IDCP than in CDCP). In addition, when the S-S was compatible, the RT was longer when the S-R was also incompatible ($p < 0.001$, $\eta_\rho^2 = 0.861$) (i.e. the RT was longer in IDIP than in CDCP). For PE (see Table 1), the repeated measures ANOVA (S-S × S-R) revealed an effect of the S-R factor (F (1, 17) = 47.6, $p < 0.001$, $\eta_\rho^2 = 0.737$), as the PE was higher in incompatible S-R trials (CDIP/IDIP) than in compatible S-R trials (CDCP/IDCP) ($p < 0.001$, $\eta_\rho^2 = 0.737$).

3.2. ERP

For the N2pc latency, the repeated measures ANOVA (S-S × S-R) did not reveal any significant effect. For the N2pc amplitude, the repeated measures ANOVA (S-S × S-R) revealed a significant effect of the S-S factor (F (1, 17) = 8.9, $p = 0.008$, $\eta_\rho^2 = 0.344$), as the N2pc amplitude was smaller when S-S was incompatible (IDCP/CDIP) than when it was compatible (CDCP/IDIP) ($p = 0.008$, $\eta_\rho^2 = 0.344$) (see Table 1 and Figs. 1f and 2a).

For the amplitude of N2cc, the repeated measures ANOVA (S-S × S-R) revealed an effect of the S-R factor (F (1, 17) = 24.5, $p < 0.001$, $\eta_\rho^2 = 0.591$), as the N2cc amplitude was larger when the stimulus was compatible (CDCP/IDCP) than when the stimulus was incompatible (CDIP/IDIP) with the response ($p < 0.001$, $\eta_\rho^2 = 0.591$) (see Fig. 2b).

4. Discussion

In the present study, two type 3 S-R incompatibilities (the direction indicated by the arrow and the stimulus position, left or right) were combined in the same task. Both irrelevant dimensions were also incompatible with each other in the IDCP and CDIP conditions (stimulus–stimulus incompatibility). Incompatibility from the position caused an interference effect (i.e. longer RT, higher PE) as did the incompatibility from the direction (causing longer RT). The electrophysiological results showed that N2pc was smaller in incompatible S-S (CDIP and IDCP) than in compatible S-S (CDCP and IDIP). This suggests the existence of S-S interference in the allocation of attentional resources to the target stimulus. The results of applying the N2pc formula to data obtained at central electrodes strongly suggest that N2pc results are not the consequence of ERP modulations occurring at central regions.

The reaction time (RT) revealed strong interference when the position of the stimulus was incompatible with the required longer response (longer RTs in incompatible position S-R –CDIP and IDIP- than in compatible position S-R –CDCP and IDCP). Furthermore, the RT revealed an interference effect when the direction was incompatible with the required response (longer RTs in incompatible direction S-R –IDCP and IDIP- than in compatible direction S-R –CDCP). Moreover, the S-S incompatibility did not increase the RT. Behavioural interference from the S-S incompatibility might have been masked by the strong interference, caused by the stimulus position, which takes place in response-related processes (Valle-Inclán, 1996). The percentage of errors (PE) was higher when the position was incompatible (in incompatible position S-R), but not when the direction indicated by the arrow was incompatible with the response (in incompatible direction S-R). There was also no effect of any interaction between both S-R incompatibilities (in IDIP). Overall, these results are consistent with the results of a previous study using a similar task (Wittfoth et al., 2009).

As regards the ERP results, the N2pc peak latency did not differ between the four conditions. However, the amplitude of N2pc was smaller in the incompatible S-S than in the compatible S-S conditions. These findings revealed interference in the visuospatial processing of the target stimulus, caused by S-S incompatibility. In other words, in the incompatible S-S conditions (IDCP and CDIP),

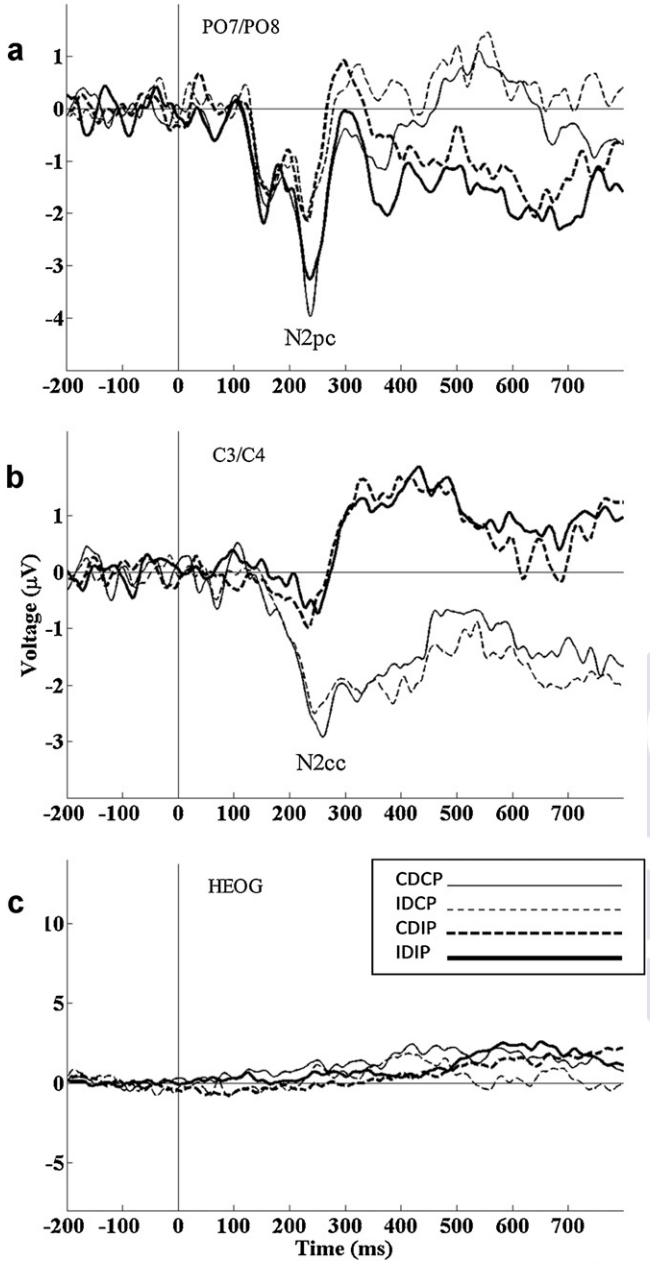

Fig. 2. Grand averages for: (a) N2pc in PO7/PO8 electrodes; (b) N2cc in C3/C4 electrodes; and (c) HEOG. Solid lines: stimulus–stimulus compatibility; dashed lines: stimulus–stimulus incompatibility; grey lines: stimulus–response compatibility due to position; black lines: stimulus–response incompatibility due to position. N2pc amplitude was smaller in incompatible S-S (IDCP and CDIP) than in compatible S-S (CDCP and IDIP); N2cc amplitude (overlapping with motor activity) was smaller in incompatible position S-R (CDIP and IDIP) than in compatible position S-R (CDCP and IDCP). HEOG did not reveal any differences in ocular movement to the stimulus position based on the experimental condition.

the direction indicated by the arrow and the position of the arrow conveyed contradictory spatial information (the arrow was pointing to the opposite hemifield with respect to its location). Thus, the irrelevant dimensions induced opposing changes in spatial attention, so that the ability to allocate attentional resources to the target stimulus was reduced in these conditions. These findings are consistent with the N2pc modulation generated by high-level properties of the display (Eimer and Kiss, 2007; Telling et al., 2009). The present results also showed that S-S incompatibility may affect the processing of the target stimulus, even when both dimensions (position and direction of the arrow) were irrelevant, unlike the conclusion made on the basis of behavioural data (see type 6 tasks in Zhang et al., 1999).

The smaller N2pc amplitude was not caused by S-R incompatibility due to the stimulus position. In that case, the amplitude of N2pc would have been smaller in incompatible position S-R (IDIP and CDIP, in which the stimulus position was incompatible with the response) than in compatible position S-R (CDCP and IDCP, in which the stimulus position was compatible with the response). The lack of N2pc amplitude modulation by S-R compatibility due to the stimulus position is consistent with the results of previous studies (Cespón et al., 2012; Praamstra, 2006; Praamstra and Oostenveld, 2003; Praamstra and Plat, 2001; Van der Lubbe and Verleger, 2002). Furthermore, the smaller N2pc amplitude was not caused by the S-R incompatibility due to the direction indicated by the arrow. In that case, the N2pc amplitude would have been smaller in incompatible direction S-R (IDCP and IDIP, in which the direction indicated by the arrow was incompatible with the response) than in compatible direction S-R (CDCP and CDIP, in which the direction pointed by the arrow was compatible with the response). Therefore, the present results allow us to exclude the possibility that the N2pc amplitude modulation was caused by any S-R incompatibility.

Previous studies showed that incompatibility due to the position of the stimulus modulates the motor activity (Valle-Inclán, 1996) as well as the N2cc (Cespón et al., 2012) when both ERP components were recorded at central regions. In addition, motor activity was also modulated by incompatibility due to the direction of the arrow (Masaki et al., 2000). Therefore, in the present study, it would be possible to relate differences in N2pc amplitude to differences in volume conduction from central regions. However, in the same temporal interval in which N2pc was measured, the amplitude of the wave recorded at central electrodes (using the N2pc derivation) was larger in compatible position S-R (CDCP and IDCP) than in incompatible position S-R (CDIP and IDIP) conditions. Taking into account that the N2pc amplitude was larger in compatible S-S (CDCP and IDIP) than in incompatible S-S (CDIP and IDCP), these results are inconsistent with the hypothesis of N2pc being modulated by volume conduction from the ERP components recorded at central regions.

It could be argued that differences in N2pc amplitude in the present task may be due to differences in the asymmetrical shape of the arrow, i.e. in incompatible S-S the arrowhead was pointing inwards while in compatible S-S the arrowhead was pointing outwards. Although the eccentricity of the arrow was the same in every condition (see Section 2), the arrowhead (i.e. the most informative portion of the arrow) was placed at a less eccentric position relative to the central cross in incompatible S-S than in compatible S-S (between 2.86° and 5.16° of visual angle in compatible S-S, and between 2.29° and 4.59° of visual angle in incompatible S-S). Several studies have shown that when the eccentricity of the stimulus increases, the N2pc amplitude decreases (Schlaghecken et al., 2001; Schaffer et al., 2011). However, the results of the present study show the opposite, i.e. that the N2pc amplitude was smaller when the arrowheads were closer to the central cross (incompatible S-S) than when the arrowheads were further away from the central cross (compatible S-S). Therefore, in the present study, the N2pc modulation appears to be explained by the S-S incompatibility, but not by the eccentricity of the arrowhead.

In accordance with the recent literature concerning N2pc (Hilimire et al., 2009, 2010; Telling et al., 2009), we interpreted the smaller N2pc amplitude as reflecting diminished target processing due to the S-S interference; however, Valle-Inclán (1996, Exp. 2) related the larger N2pc amplitude in the incompatible condition to an interference effect. This interpretation would be consistent with the ambiguity resolution theory (see Luck et al., 1997), which related increased N2pc amplitude to greater allocation of resources for suppressing the non-target stimulus. These contrary

interpretations about the N2pc modulations may be due to differences in the experimental design of the studies. Thus, in the study carried out by Valle-Inclán (1996), the stimuli (target and non-target) were presented with a very narrow degree of eccentricity (1° of visual angle from the centre of the target to the centre of the contralateral non-target stimulus), whereas in the present study, target and non-target stimuli were separated by a visual angle of 7.5°. It is therefore possible that in the present study, N2pc basically reflected processes associated with identification of the target, whereas in the task used by Valle-Inclán (1996) the N2pc may have reflected processes associated with identification of the target as well as processes associated with suppression of the distracting stimulus (see Hickey et al., 2009).

In summary, in the present study the participants carried out a Simon task with response to the colour of a lateralized arrow. The irrelevant dimensions were the position and the direction indicated by the arrow, which overlapped with the response (S-R overlaps). In addition, both irrelevant dimensions overlapped with each other (S-S overlap). Both types of S-R incompatibility caused an interference effect in the behavioural data, but they did not modulate N2pc parameters. Moreover, the N2pc amplitude was smaller in incompatible S-S than in the compatible S-S conditions. Therefore, N2pc modulations showed that the S-S incompatibility, and not the S-R incompatibilities, reduced the ability to allocate attentional resources to the target stimulus.

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2.3 Study 3 (Estudio 3)

Cespón, J., Galdo-Álvarez, S., & Díaz, F. (under review, a). Similarities and differences between interference from the stimulus position and interference from the direction pointed by the arrow. *International Journal of Psychophysiology*.

Estudios con tareas de compatibilidad estímulo-respuesta (CER) utilizaron la posición del estímulo (CER-p) y/o la dirección apuntada por una flecha (CER-d) como dimensiones irrelevantes de la tarea. A pesar de diferencias conductuales evidenciadas por el análisis de distribución de los tiempos de reacción (AD), ambas interferencias fueron asignadas a similares estadios de procesamiento, en base a similitudes en la modulación del potencial de preparación lateralizado (PPL) y de P3b. Consecuentemente, los estudios sugirieron mecanismos subyacentes similares para ambos efectos de interferencia. Sin embargo, la comparación de procesos motores asociada a cada tarea es problemática debido a que en cada una de esas tareas hay diferentes componentes implicados. Además, estudios previos usaron frecuentemente diferentes proporciones de ensayos incompatibles entre condiciones, lo que compromete la interpretación de los resultados ya que la probabilidad del estímulo puede modular P3b. Teniendo en cuenta estos problemas, en el presente estudio se analizaron los efectos de interferencia en tareas CER-p y CER-d, en las cuales los participantes tenían que responder al color de un estímulo mientras ignoraban la posición y la dirección indicada por una flecha central, respectivamente. El efecto de interferencia fue mayor en CER-p que en CER-d. El AD mostró que la posición del estímulo afectaba al rendimiento más rápidamente que la dirección de la flecha. Se observó una demora en la latencia de P3b cuando la posición era incompatible con la respuesta (tarea CER-p). Sin embargo, no se encontraron diferencias en los parámetros de P3b entre condiciones experimentales en la tarea CER-d. Por otro lado, ambos tipos de interferencia afectaron de una forma similar a los procesos relacionados con la respuesta (esto es, al potencial de preparación lateralizado en relación con la respuesta, PPL-r). Consecuentemente, en este estudio concluimos que la posición del estímulo y la dirección indicada por la flecha comparten un locus de interferencia (procesos relacionados con la respuesta) pero sólo la posición del estímulo moduló el componente P3b. Por tanto, los procesos que representan un nexo entre evaluación del estímulo y selección de la respuesta son modulados por la posición del estímulo pero no por la dirección de la flecha.

Title: Similarities and differences between interference from stimulus position and from direction of an arrow: behavioural and event-related potential measures.

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ABSTRACT

Studies with stimulus-response compatibility tasks (SRC) used the stimulus position (SRC-p) and/or the direction indicated by a central arrow (SRC-d) as irrelevant dimensions. Despite behavioural differences revealed by the distributional analyses (DA), both interferences were established at similar loci on the basis of modulations in the lateralized readiness potential (LRP) and P3b components. Consequently, similar underlying mechanisms were proposed for both interferences. However, comparison of motor processes associated with each task is problematical because each involves different components. In addition, previous studies have frequently used different proportions of trials between conditions, which complicates interpretation of the results because the stimulus probability may modulate P3b. Taking these problems into account, the present study investigated the effects of interference in SRC-p and SRC-d tasks, in which the participants responded to the colour of a stimulus while ignoring the position and the direction indicated by a central arrow, respectively. The interference was greater in the SRC-p than in the SRC-d task. The DA showed that stimulus position affected the performance more quickly than the direction of the arrow. The P3b latency was longer and the P3b amplitude was smaller when stimulus position was incompatible. However, no differences in P3b were found in the SRC-d task. Moreover, both types of interference affected response-related processes (LRP-r) similarly. Therefore, the stimulus position and the direction indicated by the stimulus may share a common locus of interference (response execution), but only stimulus position affects P3b component, which constitutes a link between stimulus evaluation and the response selection.

1. Introduction

In stimulus-response compatibility (SRC) tasks, participants respond to a stimulus feature (relevant dimension), while other features (irrelevant dimensions) must be ignored. SRC tasks are frequently used to study the interference caused by irrelevant dimensions that are incompatible with the relevant dimension of the stimulus or with the response. Eight types of SRC tasks are distinguished according to the overlap between the irrelevant and the relevant dimensions of the stimulus and between both dimensions of the stimulus and the response (see Zhang et al., 1999).

In type 3 SRC tasks, there is an overlap between the irrelevant dimension of the stimulus and the response. The Simon task is the most representative example of this type of tasks (for reviews see Leuthold, 2011; Lu and Proctor, 1995; Simon, 1990). In the Simon task, participants respond to a feature (e.g. the colour or the shape) of a spatially lateralized stimulus by pressing one of two buttons. The response buttons are also lateralized in the same spatial arrangement as the stimuli, and a slower reaction time (RT) is observed when the stimulus position (irrelevant for performing the task) is spatially incompatible with the side of the required response. This slowing in RT is known as the Simon effect.

The direction indicated by the stimulus has also been used as an irrelevant dimension that overlaps with the response, resulting in another type 3 SRC task. Thus, in a study carried out by Masaki et al. (2000), participants responded to the colour of a central arrow by pressing one of two buttons (arranged horizontally). The irrelevant dimension was the direction of the central arrow, which pointed left or right. A slower RT was observed when the direction of the arrow was incompatible with the hand of the required response (Masaki et al., 2000).

Previous studies have investigated the locus of interference for the stimulus position (SRC-p, also called Simon tasks) and the direction indicated by the stimulus (SRC-d) when they are incompatible with the response based on the task relevant feature (e.g., the colour). The response selection (De Jong et al., 1994; Masaki et al., 2000; Stürmer et al., 2002; Valle-Inclán, 1996a, 1996b) have been considered as a locus of interference for the SRC-p tasks. The lateralized readiness potential (LRP) is an event-related potential (ERP) that distinguishes between perceptual and motor stages of processing (see Coles et al., 1988 and Osman et al., 1995) and LRP modulations allowed to obtain insights about the interference locus of the SRC-d and SRC-p tasks in the response selection. Behavioural data suggested also that interference in Simon tasks took place in response execution stage (Ansorge and Wühr, 2004; Vallesi et al., 2005). Moreover, Masaki et al. (2000) carried out a detailed study of LRP modulations in a SRC-d task where the participants responded to colour of an arrow and ignored the direction pointed by that arrow. They concluded that SRC-d and SRC-p tasks affected motor processes in a similar way.

SRC-p and SRC-d tasks also modulated processes associated with P3b, which was proposed to reflect stimulus evaluation time (Donchin and Coles, 1988), although more recent evidence suggests that P3b reflects a link between perceptual analysis and response onset (Verleger et al., 2005). Longer P3b latencies have been reported in incompatible trials of SRC-p tasks (Leuthold and Schröter, 2006; Leuthold and Sommer, 1999; Melara et al., 2008; Ragot, 1990; Valle-Inclán et al., 1996a, 1996b; Van der Lubbe and Verleger, 2002) and SRC-d tasks (Masaki et al., 2000). A few studies have also reported reduced P3b amplitudes when the position is incompatible with the response (Leuthold and Schröter, 2006; Ragot, 1990; Valle-Inclán et al., 1996a, 1996b)

and when the stimuli moved towards the incompatible direction regarding the required response (Galashan et al., 2008).

Despite the similarities between incompatibility due to the stimulus position and incompatibility due to the direction indicated by the stimulus, behavioural and psychophysiological evidence also suggests differences between the loci of interference caused by both types of irrelevant dimensions.

On the one hand, interference in the incompatible condition is caused by the stimulus position (Lu and Proctor, 1995) and by the direction indicated by the arrow (Masaki et al., 2000); however, a facilitation effect in the compatible condition (faster RT in the compatible than in the neutral condition) was observed for the direction of the arrow (Masaki et al., 2000) while inconsistent results were observed for the stimulus position (for a review, see Simon, 1990). On the other hand, the distributional analysis (DA) (for a review see Proctor et al., 2011) has shown that the Simon effect is manifested at faster response times but usually decreases at slower RT (De Jong et al., 1994; Proctor et al., 2011), whereas the interference from the direction increases from faster to slower RT (Pellicano et al., 2009; Proctor et al., 2009). As a result, it has been suggested that stimulus position is processed more quickly than the direction indicated by the stimulus, probably because the direction requires processing of the symbolic meaning (Iani et al., 2011; Symes et al., 2005; Vainio et al., 2007).

Some electrophysiological differences between both tasks have also been reported. Both the N2 posterior contralateral (N2pc), which is related to visuospatial processing of the target (Luck and Hillyard, 1994), and the N2 central contralateral (N2cc), which is related to a mechanism that prevents cross-talk between the direction of the spatial attention and the manual response preparation (Cespón et al., 2012; Praamstra and Oostenveld, 2003), are present in Simon tasks (with stimuli in horizontal

arrangement) but not in SRC tasks based on the direction of central arrows. Therefore, some neurophysiological processes involved in SRC-p tasks are not present in SRC-d tasks. Moreover, in SRC-p tasks, the onset of the stimulus-locked lateralized readiness potential (LRP-s, a correlate of the covert response activation) overlaps with N2cc in similar regions and temporal windows (see Praamstra, 2007). Consequently, the covert response activation cannot be reliably measured in horizontal Simon tasks. Also, LRP-s cannot be compared between the tasks because differences may result from different components in each. In fact, studies comparing horizontal and vertical Simon tasks (Vallesi et al., 2005; Wiegand and Wascher, 2005) were criticized by Praamstra (2007) as they did not take into account that N2pc and N2cc are present in horizontal but not in vertical Simon tasks.

Results obtained for P3b modulation in SRC-d tasks are also controversial owing to the paradigm used in previous studies. Galashan et al. (2008) presented a larger number of compatible than incompatible and neutral trials, whereas Masaki et al. (2000) presented the same number of compatible and incompatible trials, but a larger number of neutral trials. Therefore, these experimental designs follow the structure of oddball paradigms, in which the subjective probability is known to influence P3b parameters (Duncan-Johnson and Donchin, 1977; Polich, 1990). In addition, it is known that Incompatible trials show reduced interference when they are preceded by another Incompatible trial (i-I sequence) while its interference is increased when they are preceded by Neutral (n-I sequence) or Compatible (c-I sequence) trials (Davelaar and Stevens, 2009; Spapé et al., 2011). Thus, when a reduced proportion of Incompatible trials are presented, the mentioned effects of sequence may modulate the effect of interference, and therefore the P3b component.

Summarizing, stimulus position attracts attentional resources in a fast way whereas that the direction of the arrow is processed more slowly since it is required the interpretation of its symbolic meaning (Abrahamse and Van der Lubbe, 2008; Klein and Ivanoff, 2011). Evidence for these differences in the speed of processing between both irrelevant dimensions was provided by the Distributional Analyses of the RTs (DA) (Proctor et al., 2011). Therefore, considering the above differences in behavioural results, can the loci of interference for both irrelevant dimensions (stimulus position and direction of the arrow) be considered equivalent?

To resolve these inconsistencies between behavioural and electrophysiological data it would be necessary to compare both incompatibilities (position and direction) using tasks with identical parameters. Also, it is necessary to take into account differences in ERP components involved on each task (i.e. N2pc and N2cc are present in the SRC-p but not in the SRC-d task) as well as those parameters of the task that might modulate any of the ERP components studied (e.g. P3b modulations might be caused by oddball designs and/or sequence effects).

The aim of the present study was to compare the behavioural and electrophysiological effects caused by the incompatibility of the stimulus position and the direction indicated by a central arrow for studying possible differences between both types of SRC interference. Thus, the participants performed an SRC task in which the stimulus position was the irrelevant dimension (SRC-p) and another SRC task in which the direction of a central arrow was the irrelevant dimension (SRC-d).

In order to make comparisons of motor processes between both tasks, the present study focused on the LRP-r. Since N2cc and N2pc are obtained in stimulus-locked averages, they are not expected to affect response-locked averages (Praamstra and Plat, 2001). In addition, in the present study the proportion of stimuli was matched between

conditions to exclude P3b modulations resulting from the use of different stimuli probabilities and/or sequence effects.

In the present study, we expected to find interference in the incompatible condition for both tasks. We also expected stimulus position to affect the performance at faster response times and that interference from the direction would have a greater effect at slower response times; we studied this by Distributional Analysis (DA) of the reaction times.

As regards the electrophysiological data, we expected to find larger differences between conditions on P3b latency and amplitude in SRC-p compared to SRC-d tasks if the position attracts more attentional resources than the direction indicated by the stimulus. Moreover, the responses were ordered on the basis of its speed and divided in fast and slow responses. According to studies using the DA, interference from the direction would be increased at slow responses while interference from the stimulus position would be maintained or decreased at slow responses. Thus, it was interesting to study P3b modulations in order to test if such modulations changed according to the magnitude of the interference.

Finally, we expected to obtain similar LRP-r modulations between conditions in both tasks, suggesting a common locus of interference for both incompatibilities at the response execution stage. The LRP-s onset was also studied in the SRC-d task to confirm whether the direction indicated by the stimulus also affected the response selection stage, as has been widely confirmed in Simon tasks.

2. Methods

2.1. Participants

Twenty-one participants (14 women, 7 men) between 19 and 28 years of age (mean age 21 years) were recruited from the local university population. The

participants volunteered to take part in the study and were paid for participating. The study received prior approval by the local ethical review board. The participants were right-handed (evaluated by the Edinburgh Handedness Inventory: Oldfield (1971)). All participants had normal or corrected to normal vision and none had any history of neurological or psychiatric disorders.

2.2. Stimuli

Two tasks were used in the present study: an SRC task based on the stimulus position (SRC-p) (see Figure 1, top) and an SRC task based on the direction indicated by a central arrow (SRC-d) (see Figure 1, bottom).

In the SRC-p task, a series of upward-pointing red or blue arrows was displayed on the screen against a black background, either on the left or on the right side of a white central cross, for both Compatible and Incompatible conditions. In the Neutral condition, the stimuli were upward-pointing red or blue arrows placed on the central cross. The arrow stimuli subtended 2.87º x 1.72º (height x width) of the visual field. In the Compatible and Incompatible conditions, the arrow stimuli were presented in parafoveal region (see Bargh and Chartrand, 2000), as the internal edge was 2.8º and the external edge 4.5º of visual angle measured from the central cross, whereas the central stimuli were presented in the foveal region. Differences in processing of the stimuli due to these eccentric positions were not expected (Cespón et al., 2012; Galashan et al., 2008; Mancebo-Azor et al., 2009). In the compatible and incompatible conditions, a geometric figure (two superimposed orthogonal bars, with the vertical bar longer than the horizontal bar, of similar size and eccentric position as the arrow) appeared in the opposite hemifield to prevent exogenous lateralization in the electroencephalogram (EEG) (see Figure 1, top).

For the SRC-d task (see Figure 1, bottom), a series of red or blue arrows pointing either left or right was displayed on the centre of the screen against a black background for the compatible and incompatible conditions. In the neutral condition, the stimuli were upward-pointing red or blue arrows placed on the central cross. The size of the arrow stimuli was identical than in the SRC-p task.

Figure 1 about here

2.3. Procedure

The participants were asked to direct their gaze towards the central cross during both tasks, and were instructed to respond to the colour of the arrow as quickly as possible by pressing one of the two buttons assigned to each colour (the response pad was a Cedrus RB-834 Model). They were also instructed to ignore the position of the arrow in the SRC-p task and the direction indicated by the arrow in the SRC-d task. In both tasks, the response buttons were arranged horizontally and were pressed with the corresponding hand (right or left) so that when the arrow pointed upwards in the central position, there was no overlap between the position and the dimension of the response, and the trials were therefore considered neutral. During the experimental session, the participants carried out different tasks (they were unrelated tasks, which did not involve S-R compatibility effects), so that the SRC-p and the SRC-d tasks were not performed consecutively. This minimized the possibility of transfer effects between the tasks. The order of presentation of the tasks was also counterbalanced.

Two blocks were presented in both tasks. In the SRC-p, in each block, each of six possible types of stimuli, grouped into three conditions with the same number of trials (80 per condition), were presented at random: Compatible Position (CP, the required response was ipsilateral to the hemifield of appearance of the target), Incompatible Position (IP, the required response was contralateral to the hemifield of

appearance of the target), and Neutral Position (NP, as described above, there was no overlap between stimulus position and response). In the SRC-d, an identical procedure was followed, resulting in 3 conditions: Compatible Direction (CD, the required response was ipsilateral with respect to the direction indicated by the arrow), Incompatible Direction (ID, the required response was contralateral with respect to the direction indicated by the arrow), and Neutral Direction (ND, there was no overlap between the direction indicated by the arrow and the required response).

In both SRC tasks, the arrows were presented for 100 ms, with 2000 ms inter-trial intervals. The short duration of presentation of the stimuli, along with the simultaneous presentation of the non target stimulus in the contralateral hemifield, minimized the probability of ocular movements towards the position of the target in the SRC-p task, when stimuli were presented at eccentric locations (see Abrahamse and Van der Lubbe, 2008). In any case, HEOG was obtained in order to ensure no differences in ocular activity between the experimental conditions.

During the experimental session, participants were seated in a comfortable chair in a dimly lit, sound-attenuated, electrically shielded chamber. Each task included a practice block of 16 trials and two experimental blocks of 120 trials each, with a resting interval of 90 s between blocks. The tasks were counterbalanced so that half of the participants were instructed to respond by pressing the button on the left with the left hand, in response to the blue arrow, and the button on the right with the right hand, in response to the red arrow, whereas the other participants were given instructions to respond in the opposite way.

2.4. Recordings

Electroencephalographic activity was recorded at the following 49 active electrode sites, in accordance with the 10-10 International System: AFz, AF3, AF4,

AF7, AF8, Fz, F3, F4, F5, F6, F7, F8, FCz, FC1, FC2, FC3, FC4, FT7, FT8, FT9, FT10, Cz, C1, C2, C3, C4, C5, C6, T7, T8, CPz, CP3, CP4, TP7, TP8, TP9, TP10, Pz, P3, P4, P7, P8, P9, P10, PO7, PO8, Oz, O1 and O2. The EEG signal was passed through a 0.01–100 Hz analogue band-pass filter, and was sampled at 500 Hz. The reference electrode was placed on the tip of the nose and the ground electrode at Fpz. Simultaneously to EEG recordings, ocular movement (EOG) recordings were obtained with two electrodes located supra- and infraorbitally to the right eye (VEOG) and another two electrodes at the external canthus of each eye (HEOG). All impedances were maintained below 10 kΩs. After signal storage, ocular artifacts were corrected off-line by use of the algorithm proposed by Gratton et al. (1983); the EEG was then segmented separately for each condition and manual response (in order to study Lateralized event-related potentials), and 1000-ms epochs (200 ms pre-stimulus baseline) were aligned to the onset of stimulus presentation whereas that response-locked epochs were established from 1000 ms before to 300 ms after the overt response. The signal was passed through a 0.01–30 Hz digital band-pass filter. Epochs with signals exceeding ±100 μV were automatically rejected, and all remaining epochs were inspected individually to identify those still displaying artifacts; the artifacted epochs were also excluded from subsequent averaging. Epochs were then corrected to the mean voltage of the 200-ms pre-stimulus recording period (baseline).

2.5. Data analysis

Trials with incorrect responses or RTs outside the 150-800 ms range were considered incorrect and were excluded. The RTs were ordered on the basis of their speed and divided, for each participant, on the percentile 50 into fast and slow RTs in order to considerate the speed of response in the statistical analyses. The RTs and percentage of errors (PE) were analysed. Three distributional analyses (DA) of the RTs

were carried out (Ratcliff, 1979) for each task (IP - CP; IP - NP; and NP - CP for SRC-p and ID - CD; ID - ND; and ND - CD for SRC-d) to determine if the magnitude of the interference, or of the possible facilitation, depended on the speed of response. For this purpose, the RTs were ordered on the basis of their speed, and for each participant, the RTs at the 4 Quintile Intersection Points that divided the distribution into 5 equal parts (quintiles) were selected. Also, interference was compared between SRC-p (IP - NP) and SRC-d (ID - ND) tasks according to the speed of the response.

For the ERP waveforms, P3b latency was measured at maximum positive peak with respect to baseline in the 300-500 ms interval at Fz, Cz, Pz and Oz sites in each task. The P3b amplitude was measured as the average amplitude between ± 50 ms around its peak latency. P3b analyses considered the speed of response as a main factor.

The stimulus-locked lateralized readiness potential (LRP-s) and response-locked lateralized readiness potential (LRP-r) were obtained for the SRC-d and the SRC-p tasks. The operation for obtaining LRP can be summarized by the following formula: [C4 – C3 (left-hand movement) + C3 – C4 (right-hand movement)] / 2 (see Coles et al., 1988 for further details about the procedure for obtaining LRP).

In the present study, the LRP-s was analysed only for the SRC-d task because the N2cc/LRP overlap present in the lateralized conditions of the SRC-p task does not allow reliable measurement of the LRP-s onset (see Praamstra, 2007). Moreover, in both tasks the waveforms may be constituted by different ERP components, which preclude comparisons between the waveforms. Nevertheless, the response-locked LRP (LRP-r) was analysed in SRC-p since N2cc is observed at stimulus-locked averages but it is expected to be jittered in response-locked averages (Praamstra and Plat, 2001).

The onset latencies of the correct response preparation in LRP-s (in the SRC-d task) and in LRP-r (in the SRC-d and SRC-p tasks) were determined using the Jackknife

procedure (Miller et al., 1998). Therefore, for LRPs, 21 different grand averages for each of the experimental conditions were computed omitting one of the participants on each grand average. Subsequently, the LRP onset was determined in the waveform of each grand average as the point in time where a 30% of the total LRP amplitude was achieved, following previous studies with Simon-type tasks (Gevers et al., 2006; Stürmer et al., 2002). Importantly, a criterion of 30% for estimating the LRP onset was recommended by Miller et al. (1998) to maximize statistic power and avoid contamination by EEG noise when (as in the present study) a high number of participants is used (e.g. 20 participants, see Miller et al., 1998). Also, when the experimental manipulation affects the initial portion of the LRP waveform, as can be observed in the LRP-r waveforms of the present study (Figure 5, bottom), this criterion for establishing the LRP onset was also recommended (see Miller et al., 1998).

In addition, in the LRP-r waveforms of the SRC-d and SRC-p tasks, mean activity between -250 and -200 ms was compared in order to study possible differences between conditions, which could be related with a positive wave observed in the Incompatible conditions.

2.6. Statistical analysis

Repeated measures ANOVAs with three within-subject factors, Task (two levels: SRC-p and SRC-d), Condition (three levels: Compatible, Incompatible, Neutral), and Speed of response (two levels: Fast, Slow) were applied to the RT and the PE data to determine any possible differences related to the experimental condition, task, and speed of response. Also, a repeated measures ANOVA with two within-subject factors, Task (two levels: SRC-p and SRC-d), and Speed of response (two levels: Fast, Slow) was carried out to compare the magnitude of the interference between both tasks according to the speed of response.

In distributional analyses, repeated measures ANOVAs with two within-subject factors, Condition (three levels: IP – CP, IP – NP and NP – CP for the SRC-p, and ID – CD, ID – ND and ND - CD for the SRC-d), and quintile intersection point (four levels: q1, q2, q3, q4) were carried out with the aim of determining whether the interference or the facilitation effects differed according to the speed of response. Also, one sample t-tests were conducted for studying if interference (i.e., IP-NP in the SRC-p task, and ID-ND in the SRC-d task) and facilitation (NP-CP in the SRC-p task, and ND-CD in the SRC-d task) were significant on each quintile intersection point.

Repeated measures ANOVAs with four within-subject factors, Task (two levels: SRC-p and SRC-d), Condition (three levels: Compatible, Incompatible, Neutral), Electrode (four levels: Fz, Cz, Pz, and Oz), and speed of response (two levels: Fast, Slow) were carried out for P3b latency and amplitude.

Repeated measures ANOVAs were carried out with two within-subject factors, Condition (three levels: Compatible, Incompatible and Neutral) and Task (two levels: SRC-p and SRC-p) to examine differences in the LRP-r onset. In the SRC-d task the covert response activation (LRP-s onset) was studied using repeated measures ANOVA with one within-subject factor, Condition (three levels: CD, ID and ND). As recommended when using the Jackknife procedure (see Ulrich and Miller, 2001), the F values were corrected according to the next formula: $Fc=F/(n-1)^2$, with Fc denoting the corrected F-value and n the number of participants.

Repeated measures ANOVA with two within-subject factors, Condition (three levels: Compatible, Incompatible and Neutral) and Task (two levels: SRC-p and SRC-d) was carried out to examine differences in mean activity of the LRP-r waveform, between -250 and -200 ms. In addition, one sample t-tests, on that mentioned temporal

window, were performed in both Incompatible conditions (IP and ID) to study whether that positivity differed from the baseline.

The Greenhouse-Geisser ε correction for the degrees of freedom was performed where necessary, and the corresponding α levels are given. When the ANOVAs revealed significant effects of the factors and their interactions, post-hoc analysis of the mean values was carried out by paired multiple comparisons (with Bonferroni corrections).

3. Results

3.1. Behavioural Measures

The repeated measures ANOVA (Task x Condition x Speed of response) revealed that the Condition had significant effects on the RT ($F(2,40) = 32.1$, $p < 0.001$) as the RT was longer in Incompatible than in Compatible trials ($p < 0.001$) and in Incompatible than in Neutral trials ($p < 0.001$). Task exerted a significant effect ($F(1, 20) = 10.2$ $p = 0.005$), as the RT was longer in SRC-p than in SRC-d ($p = 0.005$). The Task x Condition interaction also showed significant effects ($F(2, 40) = 13.2$, $p < 0.001$) as in the SRC-p the RT was longer in IP than in CP ($p < 0.001$) and in IP than in NP ($p < 0.001$); in SRC-d the RT was longer in ID than in CD ($p < 0.001$) but only marginal differences were found in ID in comparison to ND ($p = 0.060$) (see Table 1). Also, responses were faster in SRC-d than in SRC-p in the Compatible condition ($p = 0.003$), and the Incompatible condition ($p = 0.001$). The Condition x Speed of response (see Table 2) also showed an interaction effect ($F(1.50, 30.01) = 8.11$, $p = 0.003$), although Incompatible trials RTs were longer than Compatible ($p < 0.001$) and Neutral ($p < 0.001$) trials both to fast and slow responses. In addition, the Task x Condition x Speed of response also showed an interaction effect ($F(2, 40) = 6.55$, $p = 0.003$); no differences between conditions were found in SRC-d fast responses. In slow responses,

RT was longer in ID than in CD ($p < 0.001$) and ND ($p = 0.005$) conditions. In SRC-p task, RT was longer in IP than in CP (fast responses: $p < 0.001$; slow responses: $p = 0.004$) and NP (fast and slow responses: $p < 0.001$) conditions.

The repeated measures ANOVA (Task x Condition) for the percentage of errors (PE) revealed a significant effect of the Condition ($F (2, 40) = 27.7$, $p < 0.001$) as the PE was greater in the Incompatible than in the Compatible ($p < 0.001$) and than in the Neutral condition ($p < 0.001$). Task exerted a significant effect ($F (1, 20) = 5.7$, $p = 0.027$) as the PE was greater in the SRC-p than in the SRC-d task ($p = 0.027$). The interaction Condition x Task revealed significant effects ($F (2, 40) = 5.8$, $p = 0.006$) as the PE was greater in IP than in CP ($p = 0.001$) and than in NP ($p < 0.001$) in the SRC-p task whereas PE was greater only in ID than in CD ($p = 0.031$) in the SRC-d task.

Tables 1 and 2 about here

As regards the magnitude of the effect of the irrelevant dimension in the SRC-p task (see Figure 2), the repeated measures ANOVA (Condition x Quintile Intersection Point) revealed an effect of the Condition ($F (1.24, 24.9) = 39.96$, $p < 0.001$), as the effect was greater in IP – NP than in NP – CP ($p < 0.001$) as well as in IP – CP than in NP – CP ($p < 0.001$). The ANOVA did not reveal any significant effect of the factor Quintile Intersection Point.

As regards the magnitude of the effect of the irrelevant dimension in the SRC-d task (see Figure 2), the repeated measures ANOVA (Condition x Quintile Intersection Point) revealed an effect of the Quintile Intersection Point ($F (1.54, 30.86) = 4.25$, $p = 0.032$), as the magnitude of the effect was greater in the Quintile 3 than in the Quintile 1 ($p = 0.011$). The ANOVA did not reveal a significant effect of Condition, showing that facilitation and interference were present in a similar magnitude.

One sample t-tests to study on each task and quintile intersection point the interference (IP- NP, and ID-ND) and facilitation (NP-CP, and ND-CD) effects, revealed for the SRC-p task a significant interference in all the quintile intersection points ($t1\ (20) = 7.6$, $p < 0.001$; $t2\ (20) = 9.4$, $p < 0.001$; $t3\ (20) = 7.1$, $p < 0.001$; $t4\ (20) = 6.2$, $p < 0.001$) but facilitation effect was not significant in any of the quintiles. For the SRC-d task, a significant interference was found in quintile 3 ($t3\ (20) = 2.4$, $p = 0.027$) and 4 ($t4\ (20) = 2.5$, $p = 0.021$) whereas that a significant facilitation effect was found in quintile 2 ($t2\ (20) = 2.2$, $p = 0.040$), 3 ($t3\ (20) = 3.4$, $p = 0.003$), and a marginal signification was obtained in quintile 4 ($t4\ (20) = 2.1$, $p = 0.054$).

For the magnitude of the interference according to the speed of response on each task, the repeated measures ANOVA (Task x Speed of response) revealed an effect of the Task ($F\ (1, 20) = 25.20$, $p < 0.001$), as the interference was greater in the SRC-p than in the SRC-d task ($p < 0.001$). The Speed of response showed a significant effect ($F\ (1, 20) = 6.16$, $p = 0.022$), as the interference was greater at slow than at fast RTs ($p = 0.022$). Also, Task x Speed of response revealed a significant interaction effect ($F\ (1, 20) = 10.98$, $p = 0.003$). Interference was greater in SRC-p than in SRC-d task ($p < 0.001$) at fast responses; however, differences between both tasks were not significant at slow responses. Also, the interference was greater at slow than at fast responses ($p < 0.001$) in the SRC-d task whereas such differences in the magnitude of the interference were not present in the SRC-p task.

Figure 2 about here

3.2. ERP Measures

The repeated measures ANOVA (Task x Condition x Electrode x Speed of response) for P3b peak latency (see Tables 1 and 2 and Figures 3 and 4) revealed a significant effect of the Task ($F\ (1, 20) = 8.09$, $p = 0.010$), as latency was longer in the SRC-p than in the

SRC-d task ($p = 0.010$). Also, an effect of the Condition was revealed ($F (2, 40) = 20.33$, $p < 0.001$), as P3b latency was longer in Incompatible than in Compatible ($p = 0.001$) and Neutral ($p < 0.001$) conditions. In addition, Speed of response showed a significant effect ($F (1, 20) = 28.41$, $p < 0.001$), as P3b latency was longer in trials with slow responses than in trials with fast responses ($p < 0.001$). The Task x Condition interaction also showed a significant effect ($F (2, 40) = 5.81$, $p < 0.001$) as P3b peak latency was longer in SRC-p than in SRC-d task in the Incompatible condition ($p < 0.001$). In addition, the P3b latency was longer in the IP than in the CP ($p < 0.001$) and NP conditions ($p < 0.001$) in the SRC-p task, whereas it did not show significant differences between conditions in the SRC-d task. The ANOVA also showed an effect of the interaction Task x Condition x Speed of response ($F (1.56, 31.23) = 7.43$, $p = 0.004$); P3b latency was longer in the SRC-p than in SRC-d task for the Incompatible condition both at fast and slow responses ($p < 0.001$). In addition, P3b latency was longer in IP than in CP (fast responses: $p = 0.011$; slow responses: $p < 0.001$) and than in NP (fast responses: $p = 0.003$; slow responses: $p < 0.001$) conditions in the SRC-p task, whereas no differences between conditions were found in the SRC-d task.

The repeated measures ANOVA (Task x Condition x Electrode x Speed of response) for P3b amplitude (see Tables 1 and 2 and Figures 3 and 4) revealed a significant effect of the Condition ($F (2, 40) = 5.95$, $p = 0.005$), as the amplitude was smaller in the Incompatible than in the Neutral ($p = 0.017$) condition. The Task x Condition interaction also exerted a significant effect ($F (2, 40) = 4.12$, $p = 0.023$). In the SRC-p task the P3b amplitude was smaller in the IP than in the CP ($p = 0.036$) and NP ($p = 0.012$) conditions, whereas differences between conditions in P3b amplitude were not present in the SRC-d task. The ANOVA also showed an effect of the factor Electrode ($F (2.30, 46.00) = 31.70$, $p < 0.001$), as the amplitude was larger at Pz than at

Oz ($p = 0.004$), Cz ($p < 0.001$) and Fz ($p < 0.001$). The P3b amplitude was also larger at Oz than at Fz ($p < 0.001$), and it was larger at Cz than at Fz ($p < 0.001$). An effect of the Speed of the Response was also found ($F (1, 20) = 14.19$, $p = 0.001$), as P3b amplitude was larger in fast than in slow responses ($p = 0.001$).

Figures 3 and 4 about here

As regards LRP-r (see Table 1 and Figure 5), the repeated measures ANOVA (Task x Condition) for the LRP-r onset revealed a significant effect of the Condition ($F (2, 40) = 12.1$, $p < 0.001$) as the LRP-r onset was delayed in the Incompatible condition respect to the Compatible ($p < 0.001$) and Neutral ($p < 0.001$) conditions.

The repeated measures ANOVA (Task x Condition) comparing the mean activity between -250 and -200 ms in relation with the overt response, revealed an effect of the Condition ($F (2, 40) = 30.6$, $p < 0.001$), as mean activity was more positive in the Incompatible than in the Compatible ($p < 0.001$) and Neutral ($p < 0.001$) conditions. The one-sample t-tests for mean activity between -250 and -200 ms revealed a significant effect in both Incompatible conditions, that is, in IP ($t (20) = 6.6$, $p < 0.001$) and in ID ($t (20) = 3.9$, $p = 0.001$).

The repeated measures ANOVA (Condition) for the LRP-s onset in the SRC-d task did not reveal any significant effect.

Figure 5 about here

4. Discussion

In the present study, the participants carried out two stimulus-response compatibility tasks (SRC) with response to the colour of the stimuli. In one task the participants had to ignore the stimulus position (SRC based on the stimulus position, or SRC-p), and in another task, they had to ignore the direction indicated by a central arrow (SRC based on the direction of the stimulus, or SRC-d). Although both tasks

elicited interference (slower RT and higher PE in the incompatible than in the compatible conditions) and shared a common locus of interference (differences in LRP-r onset between incompatible trials compared to neutral and compatible trials as well as a transitory positive dip related to preparation of the incorrect response) in the response execution stage, the stimulus position exerted stronger interference than the direction indicated by the stimulus. This was illustrated by higher PE, interference to all responses (compared to interference only to slowed responses in SRC-d), as well as longer P3b latencies and smaller P3b amplitudes in the incompatible than in the compatible and neutral conditions only in SRC-p task. P3b results were maintained at slow responses, where the magnitude of the interference was similar in SRC-p and SRC-d tasks. Thus, P3b differences were no due to effect size. Consequently, stimulus position presented an additional locus of interference in comparison with the direction indicated by the stimulus.

Behavioural results revealed that both types of incompatibilities (SRC-p and SRC-d) elicited interference (longer RT and higher PE in the Incompatible than in the Neutral and Compatible conditions). However, greater interference was caused by the stimulus position than by the direction of the arrow, which is consistent with the findings of previous studies (Galashan et al., 2008; Wittfoth et al., 2009); a facilitation effect was only manifested in the SRC-d task.

These results were not unexpected; the presence of facilitation in compatible trials (relative to neutral trials) due to the direction indicated by the stimuli had already been reported (Galashan et al., 2008; Masaki et al., 2000); moreover, the absence of differences between Compatible and Neutral conditions in the SRC-p task were consistent with previous studies using Simon tasks with stimuli placed in horizontal arrangement (Cespón et al., 2012; Galashan et al., 2008; Praamstra and Oostenveld,

2003; but see also inconsistent results in Simon, 1990). Thus, it cannot be excluded that absence of facilitation in the SRC-p task be due to the greater complexity of the CP (where two lateralized stimuli appeared in the display) relative to the NP condition (where only a central stimulus was presented).

The DA showed a different pattern of results between SRC-p and SRC-d tasks. The interference from the stimulus position was manifested at faster RT and it was maintained at slower RT. Although the Simon effect usually decreases at slower response times (De Jong et al., 1994; Proctor et al., 2011), some studies that used the colour of the stimulus as relevant dimension showed that the interference was maintained at slower RT (Roswarski and Proctor, 1996; Wühr, 2006). According to the temporal overlap model (De Jong et al., 1994; see also Hommel, 2000), a constant interference throughout the distribution of RTs suggests that the time when participants respond to the relevant dimension (i.e. the colour) overlaps with the activation of the response to the stimulus position and this activation does not significantly decay even in the slowest responses to the colour. However, interference in SRC-d task was only manifested in slow responses, which was clearly found in the analyses of bipartition of the RT. Also, it is consistent with the results of previous studies (Pellicano et al., 2009; Proctor et al., 2009). The facilitation effect in the SRC-d task also followed the same pattern as the interference (i.e. it was not present at faster RTs although it was observed in slower responses).

The direction of the arrow did not affect the performance at faster RT, suggesting that responses to the colour occurred earlier than processing of the direction of the arrow in consistence with the temporal overlap model (De Jong et al., 1994; see also Hommel, 2000). That is, if the response to the relevant dimension is emitted before the processing of a specific irrelevant dimension then that irrelevant dimension does not

affect the performance in that specific trial. Moreover, this interpretation is consistent with the view of stimulus position orienting attention faster than the direction of the arrow (Abrahamse and Van der Lubbe, 2008; Klein and Ivanoff, 2011) since stimulus position, but not direction of the arrow, interfered in faster RTs. Some studies have attributed the slow processing of the arrow to the required semantic processing (Iani et al., 2011; Symes et al., 2005; Vainio et al., 2007).

Consequently, performance data suggest that both SRC tasks are related to an interference effect in incompatible trials, although a greater effect was found for the stimulus position than for the direction indicated by the stimulus. In addition, the interference from the position affected the performance from faster RTs while the direction of the arrow only interfered to slow RTs. The ERP results supported the existence of differences between both interference effects, providing also evidence of the cognitive processes that are the loci of interference in both tasks.

In the SRC-p task, longer P3b latency and smaller P3b amplitude were found in Incompatible than in Compatible and Neutral trials, which is consistent with previous findings showing how the Simon effect modulates P3b latency (Leuthold and Schröter, 2006; Leuthold and Sommer, 1999; Melara et al., 2008; Ragot, 1990; Valle-Inclán et al., 1996a, 1996b; Van der Lubbe and Verleger, 2002) and amplitude (Leuthold and Schröter, 2006; Ragot, 1990; Valle-Inclán, 1996a, 1996b). The present results are also consistent with the conclusion of Verleger (1997) regarding the high sensitivity of P3b latency for the Simon effect. Contrarily, P3b latency and amplitude were not affected by the experimental condition in the SRC-d task.

The results of the present study showed that P3b, which appears to reflect a link between perceptual processes and the initiation of the response (Verleger et al., 2005), was affected by incompatibility due to the stimulus position (Simon effect) but not by

incompatibility due to the direction indicated by a central arrow. Therefore, these results provided the first evidence for electrophysiological differences between both S-R incompatibilities.

The lack of modulation of the P3b latency in the SRC-d task is also consistent with the findings from studies that used semantic stimulus-response incompatibility tasks (Magliero et al., 1984; Ragot and Fiori, 1994). It could be argued that differences in P3b modulation between both tasks were due to the size effect, that is, the magnitude of the interference was greater in the SRC-p than in the SRC-d task. However, that alternative may be discarded since the results for the absence of P3b modulation in the SRC-d task remain at slow responses, where the magnitude of the interference was similar in both tasks.

The present results contrast with those of previous studies that reported modulations in P3b latency (Masaki et al., 2000) and amplitude (Galashan et al., 2008) during SRC-d tasks. The reason for these differences is probably related to differences in the experimental design. Masaki et al. (2000) reported a larger number of neutral trials than compatible and incompatible trials. Galashan et al. (2008) reported a larger number of compatible than incompatible trials, in which the effect of direction was induced by use of moving dots. In both cases, the experimental task resulted in an oddball paradigm, which has been widely related to modulate P3b amplitude. Also, Masaki et al (2000) reported an effect of interference even greater than the found at slow RTs in the SRC-d task of the present study. It might be due to the lower probability of i-I sequence, which is associated with reduced or eliminated interference in the second incompatible trial (Davelaar and Stevens, 2009; Spapé et al., 2011) in addition to the greater probability of the c-I and n-I sequences, which were associated with increased interference (Davelaar and Stevens, 2009), in the study of Masaki et al.

(2000). Therefore, in Masaki et al. (2000) the P3b modulation might be also related to the increased interference caused by sequence effects.

Regarding motor activity, LRP-r revealed interference in the incompatible condition for both tasks. This was preceded by a transitory preparation of the incorrect response in both tasks, which suggested interference in the response execution stage (Smulders and Miller, 2012) that similarly took place in SRC-p and SRC-d tasks. Also, these results are consistent with LRP-r findings in Masaki et al. (2000) using a SRC-d type task and with behavioural results from the studies of Ansorge and Wühr (2004) and Vallesi et al. (2005), which suggested that an interference locus in the response execution stage occurred in the SRC-p tasks (i.e., in the Simon tasks). Therefore, the response execution stage appears to represent a shared locus of interference for both irrelevant dimensions.

The lack of differences between both tasks in LRP-r onset suggests that N2pc and N2cc did not affect the response-locked waveforms. As this component compromises the interpretation of LRP-s in SRC-p tasks (Praamstra, 2007), it was only analysed for the SRC-d task. In this case, no differences in the onset of LRP-s between conditions were found, in contrast to results reported by Masaki et al. (2000). The discrepancies may again be explained by the greater difficulty of the task used by Masaki et al. (2000) due to the use of an oddball design. In addition to the absence of differences in P3b latency, the LRP-s results of the present study support the possibility that interference from direction, in contrast with the interference from the stimulus position, did not take place in either perceptive processes or at the response selection stage.

5. Conclusions

The present study found evidence for similarities and differences between two SRC tasks: an SRC task based on the stimulus position (SRC-p) and an SRC task based on the direction of a central arrow (SRC-d). In the incompatible condition, both irrelevant dimensions caused interference, but in the compatible condition only the direction indicated by the arrow caused a facilitation effect. Furthermore, the position interfered in fast and slow responses, while the direction affected the performance only in slow responses, suggesting that position attracts attentional resources more quickly than direction. ERP results were consistent with the differences between both tasks in the pattern of behavioural data. Specifically, interference from the stimulus position was related to longer P3b latency and smaller P3b amplitude. However, P3b was not modulated in the SRC-d task. Therefore, results from P3b provided electrophysiological evidence for differences between both S-R interferences. As regards motor processes, similar effects of interference at the response execution stage (LRP-r) were found for both stimulus-response incompatibilities. Therefore, the position and the direction indicated by the stimulus may share a common locus of interference (response execution), but the position of the stimulus also affects the stimulus categorization process and, thus, the link between stimulus evaluation and the response selection.

ACKNOWLEDGEMENTS

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Figure 1: The tasks. Top: SRC task with response to the colour (red or blue), while ignoring stimulus position (SRC-p task). From left to right, the following conditions are represented according to the position-colour compatibility: Compatible Position (CP); Neutral Position (NP); Incompatible Position (IP). Bottom: Stimulus-response compatibility (SRC) task with response to the colour (red or blue), while ignoring the direction of the arrow (SRC-d task). From left to right, the following conditions are represented according to the direction-colour compatibility: Compatible Direction (CD); Neutral Direction (ND); Incompatible Direction (ID). In both tasks, participants were instructed to press the left button with the left hand when the arrow was blue and the right button with the right hand when the arrow was red. The response buttons were counterbalanced between the participants.

Figure 2: Compatibility (interference and facilitation) effects (in ms) in the Distributional Analysis of reaction times (DA) are represented for both tasks. The upper graph represents values on each quintile intersection point for the SRC-p task: IP-CP (circles); IP-NP (squares); NP-CP (triangles). The lower graph is the same graph, but depicted for the SRC-d task: ID-CD (circles); ID-ND (squares); ND-CD (triangles).

Figure 3: s-ERP for SRC-p task (left column) and for SRC-d task (right column). Solid line: compatible conditions; dashed line: incompatible conditions: dotted line: neutral conditions. Top: P3b for the SRC-p and for the SRC-d at the Pz electrode. In the SRC-p task only, longer P3b latency and smaller P3b amplitude were observed in the Incompatible than in the Neutral and Compatible conditions. Bottom: HEOG shows absence of differences in ocular movements between conditions in each task.

Figure 4: ERP waveforms for the SRC-p task (left column) and for the SRC-d task (right column) at fast (top) and slow (bottom) responses in the Pz electrode. Solid line: compatible conditions; dashed line: incompatible conditions: dotted line: neutral conditions. P3b modulations are observed for the SRC-p task, regardless the speed of the responses. In the SRC-d task P3b modulations were not evidenced even if the magnitude of the interference at slow responses was comparable to the found in the SRC-p task.

Figure 5: LRP-s and LRP-r obtained at C3/C4 electrodes pair. Solid line: compatible conditions; dashed line: incompatible conditions: dotted line: neutral conditions. Top: LRP-s waveforms are represented for SRC-p (left) and SRC-d (right) tasks. Analysis for the SRC-d task showed absence of incorrect preparation as well as absence of differences in the onset latency of the preparation of the correct response for the ID condition. Bottom: LRP-r waveforms for SRC-p (left) and SRC-d (right). Both tasks showed signs of interference in the response execution for the incompatible condition (delayed LRP-r onset in the incompatible conditions).

Table(s)

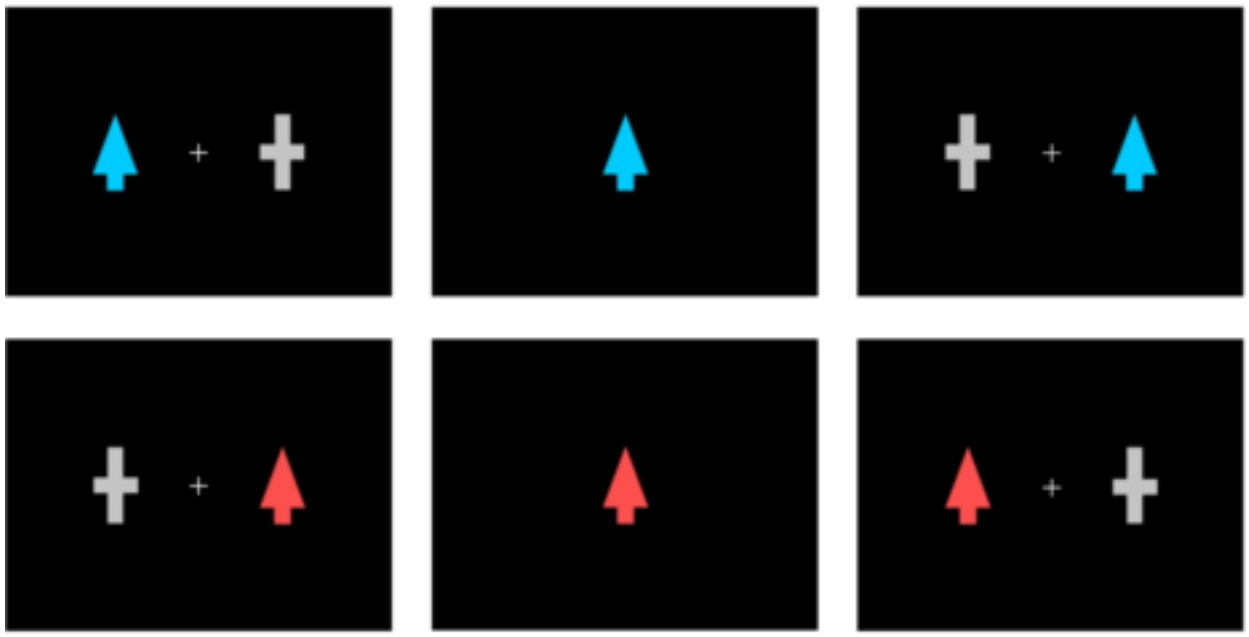
	RT	PE	P3b lat	P3b amp	LRP-r onset	LRP-s onset
SRC-P						
CP	431 (48)	4.6 (3.4)	362 (40)	13.4 (5.9)	-181 (2.7)	
NP	422 (44)	3.1 (2.9)	350 (52)	14.4 (7.6)	-181 (2.9)	
IP	461 (47)	10.5 (6.7)	413 (48)	12.1 (7.5)	-134 (2.6)	
SRC-D						
CD	380 (35)	2.6 (2.4)	353 (41)	12.1 (5.3)	-182 (3.0)	192 (2.7)
ND	392 (39)	3.8 (4.5)	351 (39)	12.6 (5.9)	-181 (2.8)	189 (2.4)
ID	404 (37)	5.3 (4.2)	349 (50)	12.0 (5.9)	-133 (2.4)	191 (2.8)

Table 1: Values in each Condition on each task (Compatible Position –CP- Incompatible Position –IP- Neutral Position –NP- for the stimulus-response compatibility (SRC) task based on the stimulus position (SRC-p) and Compatible Direction –CD- Incompatible Direction –ID- and Neutral Direction –ND- for the SRC task based on the direction of the arrow (SRC-d)) for reaction time (RT, in milliseconds), percentage of errors (PE), P300 (P3b) peak latency (in milliseconds); P3b averaged amplitude (in microvolts); onset of response-locked lateralized readiness potential (LRP-r). Also, for the SRC-d: onset of the LRP-s.

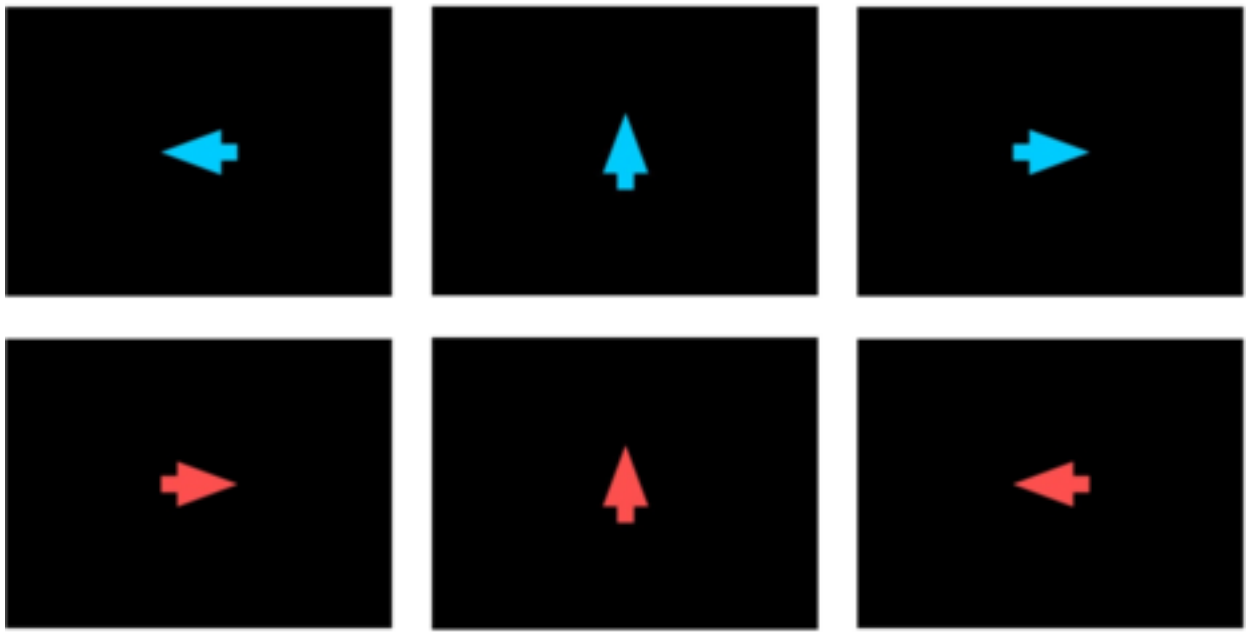
	Fast RT	Slow RT	Fast P3b lat	Slow P3b lat	Fast P3b amp	Slow P3b amp
SRC-P						
CP	340 (40)	524 (60)	350 (35)	380 (58)	15.4 (6.5)	12.2 (6.4)
NP	327 (34)	517 (61)	352 (52)	375 (55)	15.4 (7.4)	14.0 (8.6)
IP	366 (42)	556 (57)	382 (58)	449 (50)	12.6 (7.9)	11.3 (7.0)
SRC-D						
CD	302 (28)	459 (68)	341 (41)	366 (48)	13.0 (6.8)	11.8 (5.5)
ND	307 (34)	477 (66)	349 (48)	363 (41)	13.8 (5.6)	11.7 (5.7)
ID	303 (29)	503 (48)	345 (53)	374 (48)	13.4 (6.4)	11.2 (6.6)

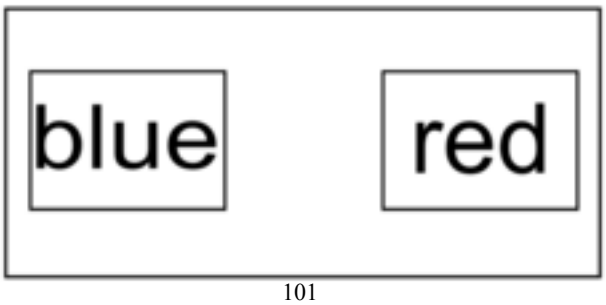
Table 2: Values in each Condition on each task (Compatible Position –CP- Incompatible Position –IP- Neutral Position –NP- for the stimulus-response compatibility (SRC) task based on the stimulus position (SRC-p) and Compatible Direction –CD- Incompatible Direction –ID- and Neutral Direction –ND- for the SRC task based on the direction of the arrow (SRC-d)) divided on the Percentile 50 according to the speed of the response. The Table shows, for fast and slow responses separately, RT (in milliseconds), P3b peak latency (in ms), and P3b averaged amplitude (in μV) (±50 ms around peak latency).

SRC-p

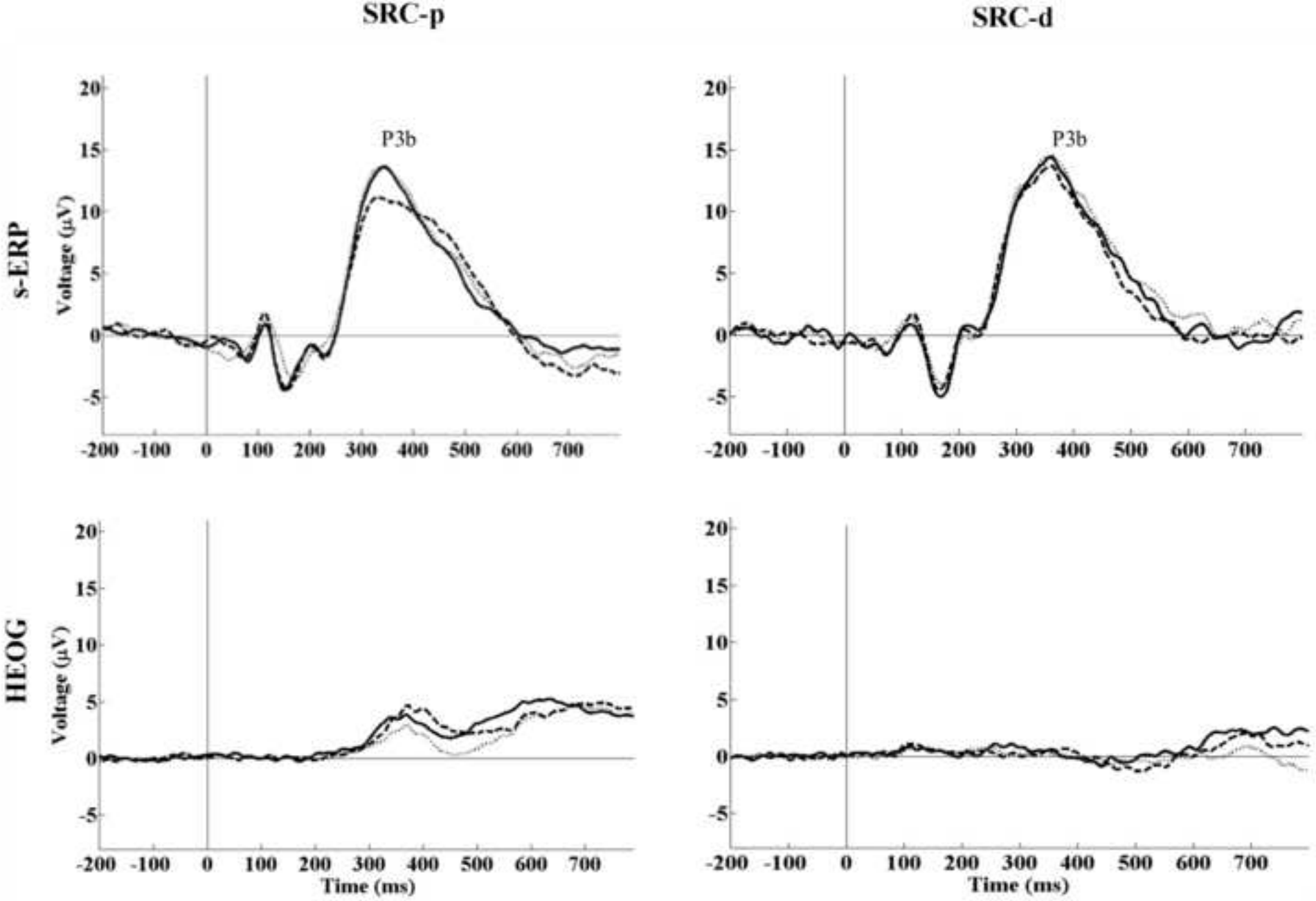


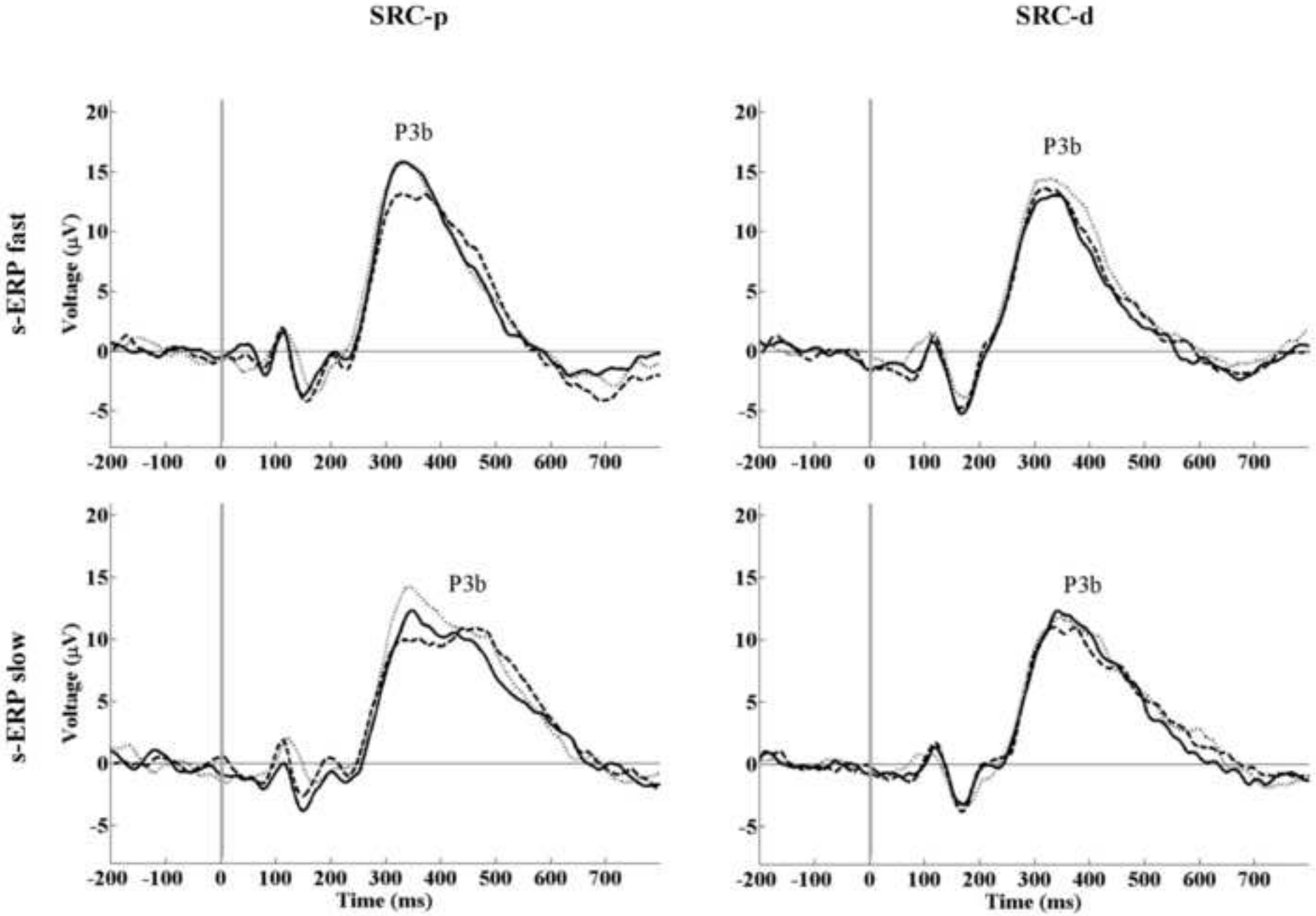
SRC-d

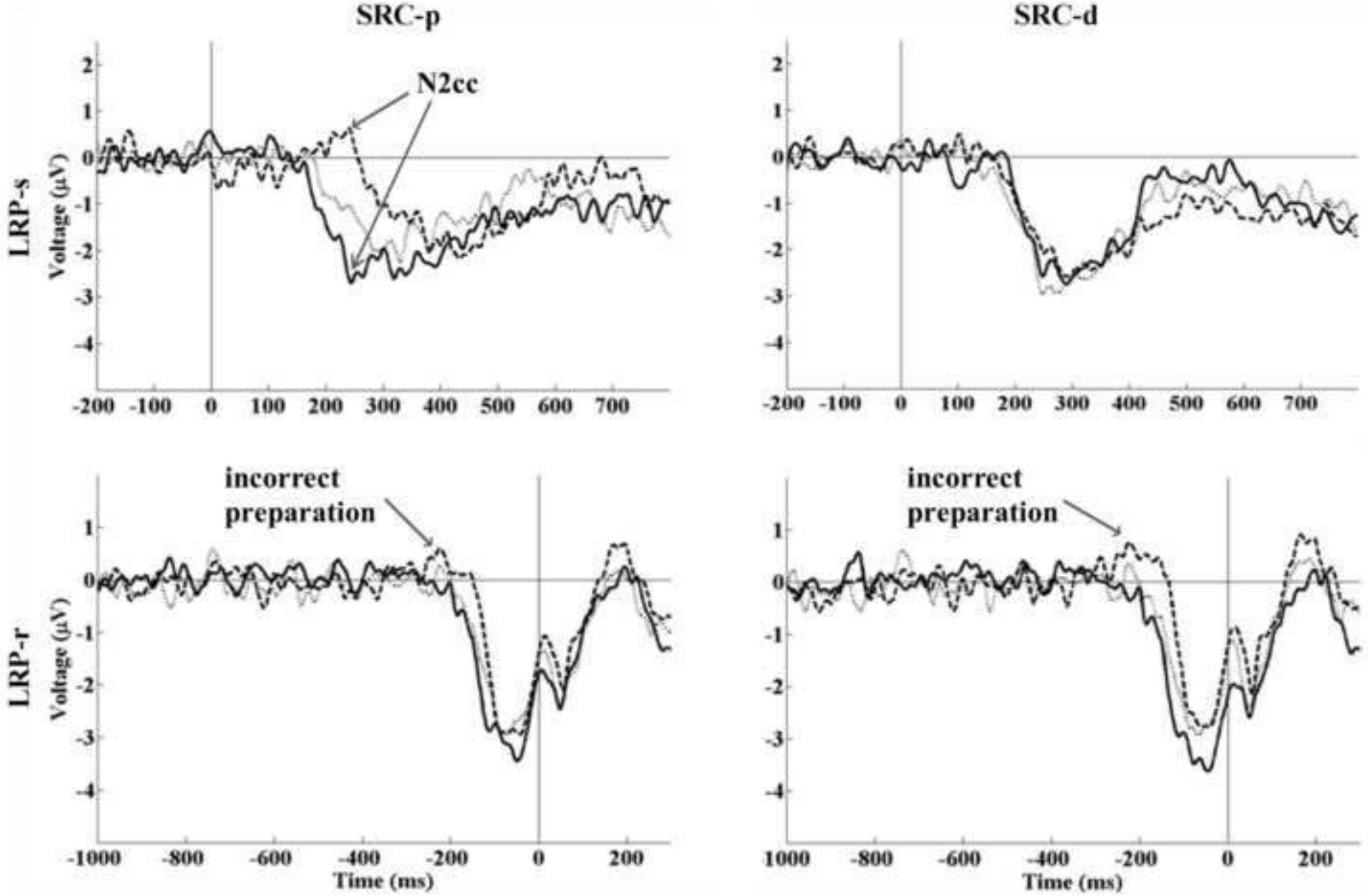




SRC-p
Compatibility effect (ms)
60
50
40
30
20
10
0
-10
-20
q1
q2
q3
q4
SRC-d
Compatibility effect (ms)
25
20
15
10
5
0
-5
q1
q2
q3
q4


SRC-p
SRC-d
s-ERP
HEOG
P3b
P3b
Voltage (μV)
Voltage (μV)
Time (ms)
Time (ms)
20
15
10
5
0
-5
-200 -100 0 100 200 300 400 500 600 700


SRC-p
SRC-d
s-ERP fast
s-ERP slow
Voltage (μV)
Time (ms)
P3b
P3b
P3b
P3b
20
15
10
5
0
-5
-200
-100
0
100
200
300
400
500
600
700


SRC-p
SRC-d
N2cc
LRP-s
LRP-r
Voltage (μV)
incorrect
preparation
Time (ms)

2.4 Study 4 (Estudio 4)

Cespón, J., Galdo-Álvarez, S., & Díaz, F. (in press). Age-related differences in ERP correlates of visuospatial and motor processes. *Psychophysiology*.

Aunque estudios previos han demostrado un enlentecimiento con la edad en procesos visoespaciales y motores, frecuentemente dichos estudios sólo han incluido una muestra de participantes jóvenes y una muestra de participantes ancianos, sin más información sobre posibles cambios relacionados con la edad en estadios intermedios del ciclo vital. El presente estudio utilizó una tarea Simon con dos dimensiones irrelevantes (posición y dirección de una flecha) para estudiar procesos visoespaciales (N2 posterior-contralateral, N2pc) y motores (potencial de preparación lateralizado en relación la respuesta, PPL-r) en muestras de adultos jóvenes (19-27 años), de mediana edad (50-64 años) y mayores (65-84 años). El tiempo de reacción y los procesos de ejecución de la respuesta motora (PPL-r) incrementaron gradualmente con la edad, mientras que los procesos visoespaciales (latencia de N2pc) mostraron enlentecimiento en mediana edad y mayores con respecto a jóvenes, sin diferencias entre los dos grupos de mayor edad. Por otro lado, no se encontraron diferencias en la magnitud de la interferencia entre los tres grupos. Además, la interferencia de la dirección sólo fue significativa en jóvenes, aunque el análisis de distribución de tiempos de reacción (AD) mostró que, en tiempos de reacción lentos, dicha interferencia también era significativa para los participantes de mediana edad. Sin embargo, con independencia del tiempo de reacción, en el grupo de mayores la interferencia de la dirección no fue significativa. Este hallazgo fue relacionado con un enlentecimiento relacionado con la edad en el procesamiento del significado simbólico de la dirección de la flecha. Esta interpretación es consistente con el hecho de que el conflicto de información espacial, producido por la incongruencia entre la información espacial conllevada por las dos dimensiones irrelevantes en las condiciones IDCP y CDIP, sólo redujo la amplitud de N2pc en el grupo de jóvenes.

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Age-related changes in ERP correlates of visuospatial and motor processes

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Abstract

Although previous ERP studies have demonstrated slowing of visuospatial and motor processes with age, such studies frequently included only young and elderly participants, and lacked information about age-related changes across the adult lifespan. The present research used a Simon task with two irrelevant dimensions (position and direction of an arrow) to study visuospatial (N2 posterior contralateral, N2pc) and motor (response-locked lateralized readiness potential, LRP-r) processes in young, middle-aged, and elderly adults. The reaction time and motor execution stage (LRP-r) increased gradually with age, while visuospatial processes (N2pc latency) were similarly delayed in the older groups. No age-related increase in interference was observed, probably related to a delay in processing the symbolic meaning of the direction in older groups, which was consistent with age-related differences in distributional analyses and N2pc amplitude modulations.

Descriptors: Event-related potentials (ERPs), Simon task, Age-related slowing, Visuospatial attention, Motor processes

Early research on the effect of aging on cognitive processes focused on behavioral measures (mainly the reaction time, RT) obtained in different experimental tasks (Cerella, 1985; Salthouse, 1985). Aging was associated with longer RTs (Salthouse, 1985). These findings led to the development of models that described the aging process as a progressive decline in cognitive functions (Birren, Woods, & Williams, 1980; Myerson, Hale, Wagstaff, Poon, & Smith, 1990).

However, subsequent cross-sectional studies provided some insight into the evolution of different subsets of cognitive processes and revealed different patterns in the effects of aging in cognitive functioning, which led to the proposal of models to explain the heterogeneity in the effects of aging on specific cognitive processes (Park et al., 2002). In this context, some processes revealed a progressive decline throughout the adult lifespan (e.g., reasoning, spatial visualization, memory, speed); however, cognitive skills, such as the amount of vocabulary known, increase up to 60 years old (Salthouse, 2009).

Longitudinal studies involving fluid cognitive skills such as visual processing, spatial orientation, or speed of processing (Finkel, Reinolds, McArdle, & Pedersen, 2003; McArdle, Ferrer-Caja, Hamagami, & Woodcock, 2002; Willis & Schaie, 2005) showed that aging was associated with a decline in these cognitive skills, starting at around 50 years old, followed by a period of relative stability and a subsequent progressive decline after 65 years old. In relation to these cognitive skills, some authors suggested that the main age-related change in brain function was the decline in the inhibition of irrelevant information, which resulted in longer RTs when irrelevant information had to be suppressed for successful performance of a task (Hasher & Zacks, 1988).

Stimulus-response compatibility tasks (SRC) (Zhang, Zhang, & Kornblum, 1999) require processes associated with fluid cognitive skills (e.g., selection of the target stimulus and inhibition of the nontargets, suppression of the irrelevant features of the target stimulus, etc.). The Simon task, where the participants respond to lateralized visual stimuli, was proposed for the study of age-related differences in such processes (Simon, 1990), as participants carry out a processing of the visual features of the display, the visuospatial orientation to the target stimulus, and a suppression of a contralateral nontarget stimulus as well as of the irrelevant dimensions of the target stimulus, among other processes. In the Simon task, participants must respond to spatially lateralized stimuli by pressing one of two buttons. The response buttons are also lateralized in the same spatial arrangement as the stimuli, with the position of the stimuli being irrelevant to the task. In those cases in which the required response is on the opposite side to the stimulus (incompatible condition), a type of interference known as the Simon effect is produced (for reviews, see Leuthold, 2011; Lu & Proctor, 1995; Simon, 1990). The interference is manifested by a longer RT in the incompatible condition than in the compatible condition, in which the response side is ipsilateral with respect to the stimulus position.

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Some evidence about the stages when cognitive decline appears in performing a Simon task was obtained. Bialystok, Craik, Klein, and Viswanathan (2004), who recruited participants between 30–80 years old, observed that RT and the Simon effect increased from the age of 60 years onward. Moreover, Juncos-Rabadán, Pereiro, and Facal (2008) found a greater interference and increased RT in participants of 50–59 years old relative to younger adults, maintenance in groups between 50–59 and 60–69 years old, and a subsequent decline at 70–82 years old. Age-related differences in Simon-type tasks are a common finding (for a review, see Proctor, Vu, & Pick, 2005). Nonetheless, other studies did not find age-related differences in the Simon effect (Kubo-Kawai & Kawai, 2010; Proctor, Pick, Vu, & Anderson, 2005). Such discrepancies are usually attributed to factors related to the experimental design. Specifically, Proctor et al. (2005) suggested that the difficulty for older participants lay in the suppression of the irrelevant dimension when it came from the same source of stimulation as the relevant dimension. Thus, when relevant and irrelevant dimensions belonged to different physical stimuli, age-related differences were not present. Moreover, Kubo-Kawai and Kawai (2010), in a study combining Simon and go/no-go tasks, suggested that greater task difficulty slowed RTs and cancelled the age-related differences.

However, the RT measure is the final outcome of many cognitive processes involved in performing a task (e.g., different subprocesses associated with stimulus processing, selection of an appropriate response, and execution of the selected response). Event-related brain potentials (ERPs) provide a high-resolution measure of brain activity and appear suitable for studying the electrophysiological correlates of cognitive processes to establish which processes decline with age. Moreover, ERP technique is an appropriate approach in the study of cognitive control and enables age-related differences in correlates of cognitive control to be demonstrated even when decline in behavioral performance is still not evident (Vallesi & Stuss, 2010).

ERP studies have demonstrated that behavioral slowing is not the result of a homogeneous decline in cognitive processes, supporting the above concept of heterogeneity in the decline pattern of the cognitive processes (Park et al., 2002). In fact, no differences between young adults and healthy elderly participants in ERP correlates of perceptual processes were found in studies using a variety of cognitive tasks, such as the oddball task (Amenedo & Díaz, 1998), facial recognition tasks (Chaby, George, Renault, & Fiori, 2003; Galdo-Álvarez, Lindín, & Díaz, 2009; Pfütze, Sommer, & Schweinberger, 2002), and SRC tasks (Falkenstein, Yordanova, & Kolev, 2006; Kolev, Falkenstein, & Yordanova, 2006).

Furthermore, an important locus of age-related slowing was manifested in the motor-generating system using SRC tasks (Falkenstein et al., 2006; Kolev et al., 2006; Roggeveen, Prime, & Ward, 2007; Wild-Wall, Falkenstein, & Hohnsbein, 2008; Yordanova, Kolev, Hohnsbein, & Falkenstein, 2004) and mental rotation tasks (Band & Kok, 2000). Electrophysiological evidence for this was provided by measurement of the lateralized readiness potential (LRP), a component that, through a subtraction procedure, isolates an increase of activity at electrode sites contralateral to the hand involved in preparing a movement. The time from stimulus presentation to the LRP onset (LRP-s) can be used as a measure of the stimulus processing prior to the moment when response activation starts. Likewise, the interval between the LRP onset and the overt response (LRP-r) can be considered as an index of the duration of the response activation (Smulders & Miller, 2012).

Some studies showed that the LRP amplitude was larger in elderly than in young participants (Roggeveen et al., 2007; Wild-Wall et al., 2008; Yordanova et al., 2004). It was proposed that larger LRP amplitudes in elderly participants are related to decline in inhibitory control (Roggeveen et al., 2007). Moreover, other studies (Wild-Wall et al., 2008; Yordanova et al., 2004) suggested that larger LRP amplitudes might be related to an increased threshold of response activation due to dysregulation in high-level control systems. In addition, some studies have reported earlier response-locked LRP (LRP-r) latencies in elderly than in young participants (Falkenstein et al., 2006; Kolev et al., 2006; Roggeveen et al., 2007; Wild-Wall et al., 2008; Yordanova et al., 2004). This finding may reflect a need for a longer activation of the motor cortex in elderly participants to enable the response to be executed (Kolev et al., 2006). Alternatively, prolonged execution of the motor response has also been related to an age-related strategy emphasizing response accuracy (Osman et al., 2000).

Visuospatial processes are considered another important source of age-related slowing, as manifested in delayed N2pc latencies in SRC tasks (Van der Lubbe & Verleger, 2002) and visual search tasks (Amenedo, Lorenzo-López, & Pazo-Álvarez, 2012; Lorenzo-López, Amenedo, & Cadaveira, 2008; Lorenzo-López et al., 2011). The N2pc is a negative ERP component recorded at parietal sites contralateral to the visual hemifield where the target stimulus is located, with maximum amplitude between 200–300 ms after stimulus presentation (Eimer, 1996; Luck & Hillyard, 1994; Woodman & Luck, 1999, 2003). N2pc has been associated with visuospatial processing of the target stimulus and with inhibition of the nontarget (see Hickey, Di Lollo, & McDonald, 2009).

Despite the above evidence, very few ERP studies have attempted to investigate the modulation of the cognitive processes throughout the lifespan, and most studies have simply compared groups of young and elderly adults.

The present study included a Simon-like task, in which participants were required to respond to the color of a lateralized arrow but to ignore the position of the arrow and the direction indicated by the arrow (see Figure 1). Thus, four experimental conditions were generated according to the compatibility or incompatibility between the two irrelevant dimensions and the required response: compatible direction and compatible position (CDCP), incompatible direction and compatible position (IDCP), compatible direction and incompatible position (CDIP), incompatible direction and incompatible position (IDIP). This task enabled examination of the electrophysiological correlates of visuospatial processing of the target stimulus (N2pc). The task also provides a correlate of the execution of the motor response: the LRP-r. The LRP-r onset and amplitude may provide information about the interference elicited by the irrelevant dimensions.

The inclusion of two irrelevant dimensions was expected to increase task difficulty, which according to previous studies (Juncos-Rabadán et al., 2008) would lead to increased age-related differences. Moreover, as in the IDCP and CDIP conditions, the arrow conveys contradictory spatial information (i.e., the arrow points towards the opposite hemifield to where it is located) (see Figure 1), the present task enables the study of the perceptual conflict. On the basis of a previous study in a sample of young participants (Cespón, Galdo-Álvarez, & Díaz, 2013) and consistent with studies that used N2pc as a tool to study the strength of irrelevant stimuli to attract attentional resources (Eimer & Kiss, 2007; Hickey, McDonald, & Theeuwes, 2006), perceptual conflict would be related to smaller N2pc amplitude in IDCP and CDIP conditions (where the two irrelevant dimensions conveyed contra-

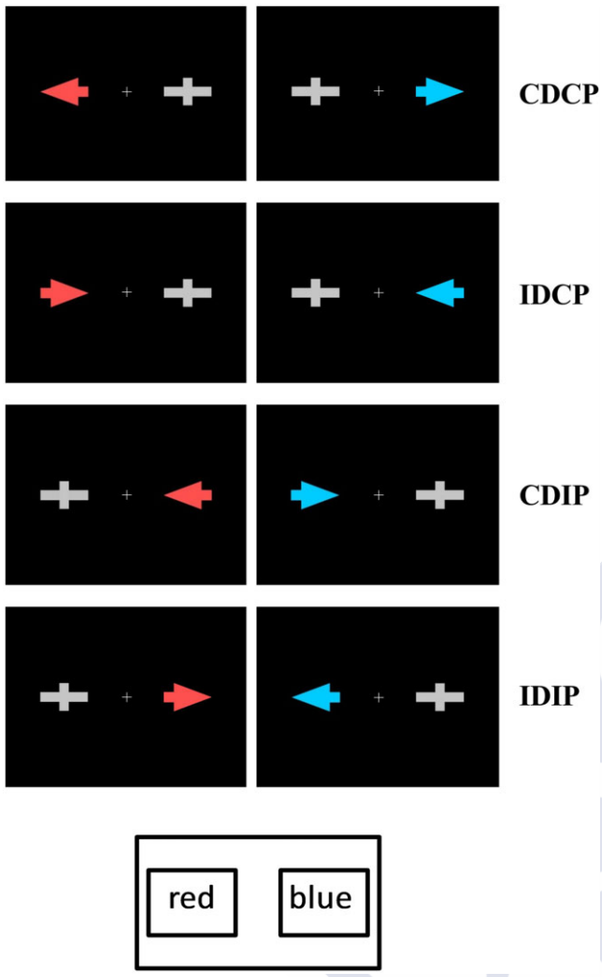

Figure 1. Stimuli presented and response buttons. Participants were instructed to respond by pressing the left button with the left hand when a red arrow appeared, and the right button with the right hand when a blue arrow appeared, so that the conditions presented (from top to bottom rows) were, respectively: compatible direction and compatible position (CDCP), incompatible direction and compatible position (IDCP), compatible direction and incompatible position (CDIP), and incompatible direction and incompatible position (IDIP). The response buttons were counterbalanced between participants.

dictory spatial information) than in CDCP and IDIP conditions (where the two irrelevant dimensions conveyed the same spatial information) (see Figure 1).

According to the cognitive slowing theory (Salthouse, 2009), age-related slowing in ERP correlates of visuospatial (N2pc latency) and motor (LRP) processes was expected (see Figure 2.1a and 2.2a). According to the inhibitory deficit hypothesis (Hasher & Zacks, 1988), age-related increases in S-R interference between the irrelevant dimensions and the response to the color (revealed by RTs and LRP data) and perceptual conflict (revealed by N2pc amplitude) were expected (see Figure 2.3a and 2.4a).

As far as we know, this is the first ERP study focusing on effects of aging on ERP correlates of visuospatial and motor processes including a sample of middle-aged participants. Nonetheless, previous behavioral reports related to cognitive slowing (Salthouse, 2009) and the interference effect (Juncos-Rabadán et al., 2008) in middle-aged participants led us to expect a decline in the cognitive functioning in middle-aged relative to young participants, which would be more evident in the elderly group.

Method

Participants

Forty-five participants (30 women, 15 men) between 19 and 84 years old were divided into three age groups: young group, 19–22 years old (mean age 20.5 years); middle-aged group, 50–64 years old (mean age 56.0 years); elderly group, 65–84 years old (mean age 71.1 years). Each group comprised 15 participants. The participants were recruited from the general population (for more details about the sample, see Table 1) and volunteered to take part in the study. The study received prior approval by the local ethical review board. Forty-four of the participants were right-handed and one was ambidextrous (evaluated by the Edinburgh Handedness Inventory; Oldfield, 1971). All participants had normal or corrected-to-normal vision. The participants had no history of neurological or psychiatric disorders according to self-report.

Task

A series of red or blue arrows pointing either left or right was displayed on a screen against a black background. The screen was placed 100 cm in front of the participants. The arrow stimuli subtended 2.87° horizontally and 1.72° vertically in the visual field, and the arrows were presented in the parafoveal region (the internal edge was 2.29° and the external 5.16° of visual angle regarding a central cross: see Bargh & Chartrand, 2000). A gray geometric figure of similar morphology and eccentric position (two orthogonally superimposed bars, the vertical thicker than the horizontal, see Figure 1) was presented in the opposite hemifield to the target stimulus. The arrows (and the contralateral stimulus) were presented for 125 ms, with 2,000-ms intertrial intervals. The participants were instructed to direct their gaze towards the central cross throughout the task, which, together with the short interval during which the stimuli were presented, minimized the likelihood of ocular movements towards the area where the arrow appeared (see Abrahamse & Van der Lubbe, 2008).

Procedure

Each participant carried out the task while seated in a comfortable chair in a dimly lit, sound-attenuated, electrically shielded chamber. The participants were instructed to respond to the color of a blue or red arrow by pressing one of two horizontally positioned buttons (blue or red), but to ignore the position and the direction indicated by the arrow (Figure 1). The arrow was presented on either side of the central cross (where the participants were asked to direct their gaze throughout the task) and pointed either to the left or to the right. The two irrelevant dimensions (position and direction indicated by the arrow) gave rise to four experimental conditions, depending on whether the dimensions were compatible or incompatible with the response to the color: CDCP, IDCP, CDIP, and IDIP (Figure 1). The same numbers of trials were run for all four conditions (80 per condition).

After a practice block of 24 trials, a total of 320 trials (80 per condition) were presented in two blocks, with an interblock interval of 90 s. The response hand assigned to each color of the stimulus

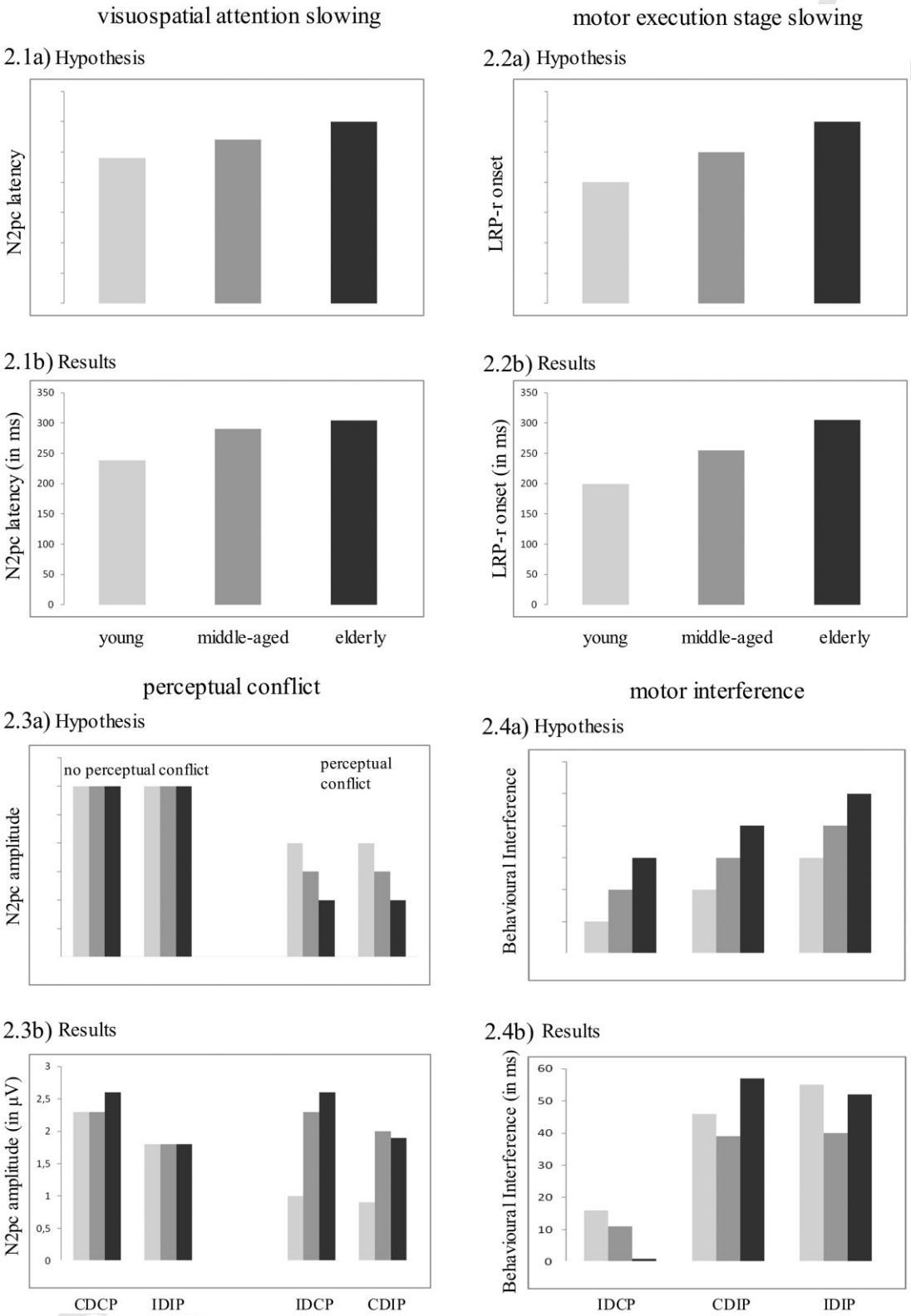

Figure 2. Main hypotheses and results graphically represented through diagrams (light bar chart: young participants; gray bar chart: middle-aged participants; dark bar chart: elderly participants). Age-related slowing in visuospatial (2.1a) and motor (2.2a) processes was hypothesized. The results showed that the motor execution stage (LRP-r onset) was progressively lengthened with age (2.2b), whereas visuospatial attention processes (N2pc latency) were slowed in middle-aged and elderly regarding young participants but differences were not present between the older groups (2.1b). On the other hand, age-related reduction of N2pc amplitude was hypothesized in those conditions where perceptual conflict was present (i.e., IDCP and CDIP) (2.3a) as well as an increased motor interference with age (2.4a). The results showed that only in young participants the N2pc was smaller in those conditions where perceptual conflict was present (2.3b), probably because the arrow direction only affected the performance in the young group (2.4b). S-R interferences did not increase with age (2.4b).

Table 1. *Main Characteristics of Sample Size*

	Sample size	Females / males	Range age	Average age	Years of schooling
Young	15	10 / 5	19–23	20.5 (1.2)	14.4 (4.3)
Middle-aged	15	10 / 5	51–63	56.0 (4.5)	14.4 (1.2)
Elderly	15	10 / 5	65–84	71.1 (5.9)	13.4 (3.5)

Note. Mean and standard deviation values are provided for age and years of schooling.

was counterbalanced among the participants, who were instructed to respond as quickly and accurately as possible.

EEG Recordings

In total, 47 active electrodes were used for the electroencephalogram (EEG) recordings, in accordance with the International 10-10 system: AFz, AF7, AF8, Fz, F3, F4, F5, F6, F7, F8, FCz, FC1, FC2, FC3, FC4, FT7, FT8, FT9, FT10, Cz, C1, C2, C3, C4, C5, C6, T7, T8, CPz, CP3, CP4, TP7, TP8, TP9, TP10, Pz, P3, P4, P7, P8, P9, P10, PO7, PO8, Oz, O1, and O2. The EEG signal was passed through a 0.01–100 Hz analog band-pass filter and was sampled at 500 Hz. The reference electrode was placed on the tip of the nose and the ground electrode at Fpz. Simultaneously to EEG recordings, ocular movement (electrooculogram [EOG]) recordings were obtained with two electrodes located supra- and infraorbitally to the right eye (VEOG) and another two electrodes at the external canthus of each eye (HEOG). All impedances were maintained below 10 kΩs.

After signal storage, a two-step procedure was used to remove epochs with horizontal ocular artifacts, following a procedure used in previous studies (e.g., Woodman & Luck, 2003). Firstly, trials with large horizontal eye movements (larger than ± 35 μV) were removed. Secondly, averaged HEOG waveforms showing residual eye movements (HEOG activity exceeding ± 3 μV) were eliminated. Also, blinks were corrected offline by use of the algorithm of Gratton, Coles, and Donchin (1983).

The signal was passed through a 0.01–30 Hz digital band-pass filter. One-second epochs were extracted: 200 ms prestimulus in stimulus-locked ERPs (N2pc, LRP-s) and 700 ms preresponse in response-locked ERPs (LRP-r). Epochs with signals exceeding ± 100 μV were automatically rejected, and all remaining epochs were inspected individually to identify those still displaying artifacts; the artifact epochs were also excluded from subsequent averaging. Epochs were then corrected to the mean voltage of the baseline (–200 to 0 in stimulus-locked ERPs, –700 to –500 in response-locked ERPs). For stimulus-locked ERPs, the number of averaged epochs per condition for each group was as follows: 63 (young group), 61 (middle-aged group), 62 (elderly group). For each hemifield and condition, only those participants with a minimum of 26 epochs after artifact rejection were included in the analyses (range: 26–40). The number of averaged epochs per condition for response-locked ERPs was as follows: 65 (young group), 69 (middle-aged group), 69 (elderly group).

Data Analysis

Trials with incorrect responses or RT outside the 100–1,000 ms range were excluded from the behavioral and ERP analyses. The percentages of trials excluded because of responses that were too slow were as follows: 0.003% young; 0.006% middle-aged; 0.29% elderly.

The RT, the subtracted interference on each incompatible condition (i.e., IDCP – CDCP, CDIP – CDCP, and IDIP – CDCP) and the percentage of errors (PE) were analyzed. To determine whether the magnitude of the interference depended on the speed of response, distributional analysis (DA) of the RTs was carried out (Ratcliff, 1979) for each group (young, middle-aged, elderly) and type of interference (IDCP, CDIP, IDIP). For this purpose, the RTs were ordered by length, and for each participant, the RTs at the four quintile intersection points (QIPs) that divided the distribution into five equal parts (quintiles) were selected.

In order to obtain the LRP waveforms (LRP-s and LRP-r), the difference in contralateral-ipsilateral activation for C3 and C4 electrode pairs in each hemisphere was calculated. The differences were then averaged (Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988). The method can be summarized by the following formula: $[(C4 - C3)_{\text{left hand movements}} + (C3 - C4)_{\text{right hand movements}}] / 2]$. The N2pc component was obtained on the basis of the hemifield of presentation of the stimulus by the following formula: $[(PO8 - PO7)_{\text{left hemifield}} + (PO7 - PO8)_{\text{right hemifield}}] / 2]$.

The N2pc component was identified as the larger negative peak between 200–350 ms after the stimulus presentation at the PO7/PO8 electrode pair. The N2pc amplitude was calculated as the mean amplitude within ± 30 ms around peak latency for each participant. In order to study possible differences in the N2pc onset, a procedure similar to that used by Van der Lubbe and Verleger (2002) was used. Specifically, the averaged amplitudes in three consecutive temporal windows of 25 ms (i.e., 125–150, 150–175, and 175–200) were obtained.

The onset latency of the correct preparation in the LRP-r was determined by the method of Schwarzenau, Falkenstein, Hoormann, and Hohnsbein (1998), which assumes that the onset of correct preparation corresponds to the intersection point of two straight lines, one fitted to the baseline and another to the rising slope of the LRP.

LRR-r onsets were subtracted as follows: IDCP – CDCP, CDIP – CDCP, and IDIP – CDCP to study if possible delays in LRP-r onset for S-R incompatible (IDCP, CDIP, and IDIP) relative to compatible condition (CDCP) increased with age.

Effects of the irrelevant dimensions on the peak latency of the LRP-s, measured as the maximum negative peak between 300–650 ms after stimulus presentation, were studied. The LRP-s amplitude was measured as the mean amplitude within ± 30 ms around peak latency. The onset of the LRP-s could not be reliably measured in the present study because, when lateralized stimuli are presented in horizontal arrangement, a central contralateral negativity (N2cc) overlaps with the LRP-s onset (Cespón, Galdo-Álvarez, & Díaz, 2012; Praamstra, 2007). However, LRP-r onset can be studied because N2cc is a stimulus-related component, and therefore it is not expected to affect response-related averages (Praamstra & Plat, 2001). Simon tasks designed with the aim of studying the LRP-s onset usually present the stimuli in a

Table 2. *Summary of Behavioral and Electrophysiological Results*

	RT	PE	N2pc lat	N2pc amp	LRP-r onset	LRP-s lat	LRP-s amp
CDCP young	404 (41)	2.9 (2.7)	240 (26)	−2.3 (1.5)	−245 (60)	349 (36)	2.2 (1.7)
IDCP young	420 (50)	4.0 (2.9)	233 (31)	−1.0 (0.9)	−211 (53)	398 (66)	2.0 (1.1)
CDIP young	450 (42)	6.4 (5.0)	241 (28)	−0.9 (1.2)	−174 (59)	404 (76)	1.9 (1.4)
IDIP young	459 (47)	9.4 (4.7)	240 (19)	−1.8 (1.0)	−168 (47)	412 (80)	1.9 (1.9)
CDCP middle-aged	511 (70)	1.5 (1.5)	277 (29)	−2.3 (1.8)	−290 (56)	402 (59)	4.1 (1.4)
IDCP middle-aged	522 (62)	2.8 (3.1)	295 (26)	−2.3 (1.5)	−280 (50)	409 (58)	4.3 (1.3)
CDIP middle-aged	550 (69)	3.9 (4.2)	289 (31)	−2.0 (1.4)	−228 (50)	472 (54)	3.4 (1.6)
IDIP middle-aged	551 (59)	4.5 (7.2)	299 (43)	−1.8 (1.4)	−222 (37)	487 (64)	3.6 (1.5)
CDCP elderly	573 (92)	1.3 (2.0)	310 (35)	−2.6 (1.5)	−341 (59)	457 (74)	4.2 (2.3)
IDCP elderly	573 (87)	1.9 (2.9)	302 (22)	−2.6 (1.9)	−326 (82)	458 (75)	3.7 (1.9)
CDIP elderly	630 (86)	6.1 (5.3)	300 (31)	−1.9 (2.5)	−273 (56)	539 (76)	3.2 (1.6)
IDIP elderly	625 (85)	5.0 (3.4)	304 (36)	−1.8 (1.8)	−279 (55)	536 (92)	3.1 (1.8)

Note. Means (standard deviations) are shown. CDCP = compatible direction–compatible position; IDCP = incompatible direction–compatible position; CDIP = compatible direction–incompatible position; IDIP = incompatible direction–incompatible position; young (19–23 years); middle-aged (50–64 years); elderly (older than 65 years); RT = reaction time (in ms); PE = percentage of errors; lat = latency; amp = average amplitude; LRP-r = response-locked lateralized readiness potential; LRP-s = stimulus-locked lateralized readiness potential.

vertical arrangement, although this setting does not allow study of the N2pc component.

Statistical Analysis

RTs were analyzed and linear regression analyses were conducted to test age-related slowing. In addition, LRP-r onset latency, LRP-s peak latency, and N2pc onset and peak latencies were studied to provide information about age-related slowing in correlates of motor and visuospatial processes. Moreover, age-related differences in S-R interference were studied by subtracting the compatible from the incompatible conditions (i.e., IDCP – CDCP, CDIP – CDCP, and IDIP – CDCP) in RTs and LRP-r onset. Also, the PE was studied. The DA also enabled study of the temporal dynamic of the interferences on each group. In addition, perceptual interference was studied by means of N2pc amplitude modulations.

In order to determine any differences in RTs, PE, LRP-r onset latency, N2pc onset latency, and in the latencies and amplitudes of N2pc and LRP-s components based on the experimental conditions and the age, mixed analyses of variance (ANOVAs) were carried out with two within-subject factors, position (two levels: compatible and incompatible) and direction (two levels: compatible and incompatible), and one between-subject factor, age (three levels: young, middle-aged, and elderly).

To evaluate the LRP-r positive deflection observed in young participants, one-sample *t* tests were applied to the mean values of five consecutive windows of 50 ms each, with a step size of 10 ms between windows (i.e., each window had an overlap of 40 ms with the prior window) and starting 45 ms before the LRP positive peak. If all of the windows reached a significant value, we can conclude that the waveforms deviated significantly from baseline.

To evaluate the magnitude of the interference in RTs and LRP-r onset latency, mixed ANOVAs were carried out with one within-subject factor, condition (three levels: IDCP, CDIP, and IDIP), and one between-subject factor, age (three levels: young, middle-aged, and elderly). In addition, to study whether the interference was significant in each QIP, one-sample *t* tests were carried out for each type of interference on each group of participants.

Linear regressions were conducted for each condition separately in middle-aged and elderly participants, with the age of the participants as the independent variable and RT, LRP-r onset latency (using absolute values), and N2pc peak latency as dependent variables. Linear regression analysis was also carried out with the age of the participants as the independent variable and the averaged values among the four conditions of RT, LRP-r onset latency, and N2pc peak latency as dependent variables. Coefficients of determination and *F* significant values are reported.

Pearson correlation analysis between RT and the latency of each component was conducted separately for each experimental condition in the middle-aged and elderly groups, to study correlations between delays in RT and delays in visuospatial (N2pc) and/or motor execution (LRP-r) processes (using absolute values). Pearson correlation analysis was also carried out by averaging the values of RT and ERP latencies among the conditions. The group of young participants was not included in linear regression and correlation analyses since this would require a group of participants between 30 and 49 years old.

The Greenhouse-Geisser ε correction value for the degrees of freedom was used when necessary, and the corresponding α levels were determined. When the ANOVAs revealed significant effects due to the factors and their interactions, post hoc comparisons of the mean values were carried out by paired multiple comparisons (adjusted to Bonferroni).

Results

Behavioral Measures

Slowing. For the RT (see Table 2), the mixed ANOVA (Position × Direction × Age) revealed a significant effect of age, $F(2,42) = 23.3$, $p < .001$, as the RT was shorter in young than in middle-aged ($p < .001$) and elderly groups ($p < .001$). The RT was also shorter in middle-aged than in elderly participants ($p = .029$). Position had a significant effect, $F(1,42) = 311.0$, $p < .001$, as the RTs were shorter for trials with compatible position than for trials with incompatible position ($p < .001$). The Direction × Age interaction was significant, $F(2,42) = 4.0$, $p = .026$, as the RT was shorter when direction was compatible than when it was incompatible ($p = .002$) in the young adults, whereas no differences were found in middle-aged ($p = .115$) and elderly ($p = .479$) groups.

Linear regression showed a significant linear relationship between RT and age of the participants for each experimental condition: CDCP: $R^2 = .271$, $F(1,29) = 10.4$, $p = .003$; IDCP: $R^2 = .308$, $F(1,29) = 12.5$, $p = .001$; CDIP: $R^2 = .358$, $F(1,29) =$

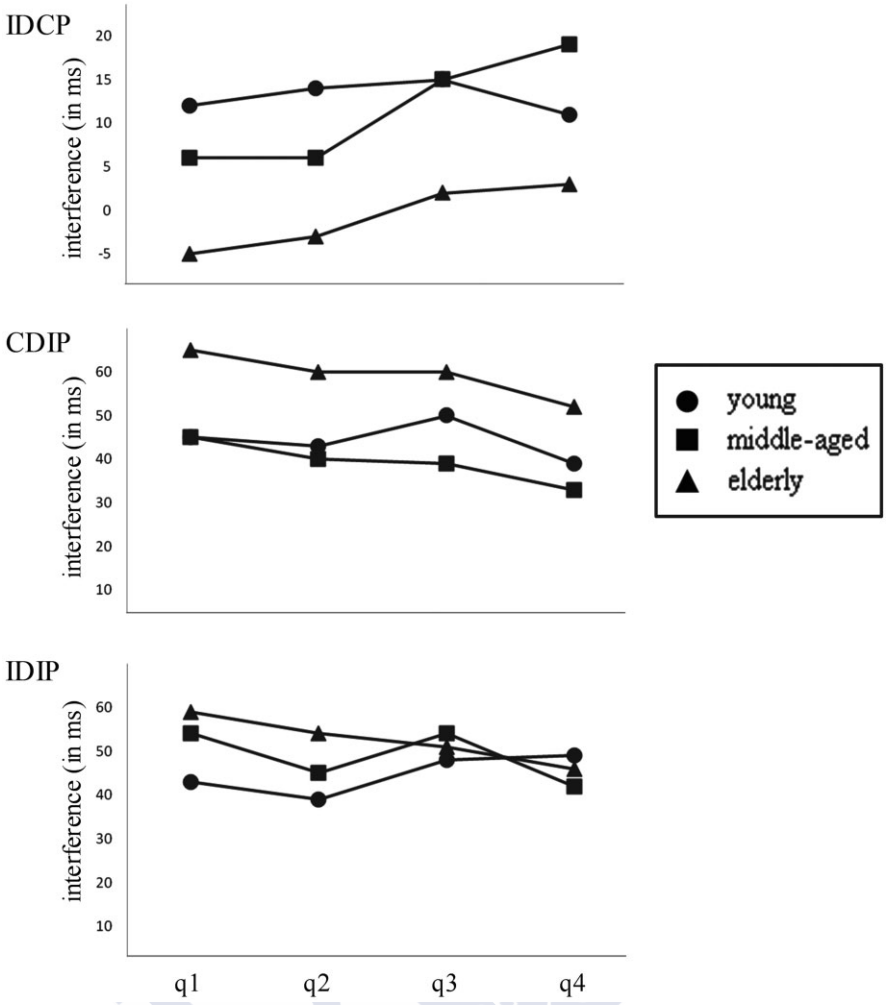

Figure 3. Distributional analyses of the RTs for each group of participants. Interference from the CDIP and IDIP conditions was present independently of the speed of response for the three age groups. In IDCP, interference was present for young participants in QIP1, QIP2, and QIP3. For middle-aged participants, interference in the IDCP was manifested at slow responses (QIP3 and QIP4). Interference in IDCP was not observed in elderly participants.

15.6, $p < .001$; IDIP: $R^2 = .375$, $F(1,29) = 16.8$, $p < .001$. Linear regression also revealed a significant linear relationship between RT (averaged among the four experimental conditions) and age of the participants, $R^2 = .336$, $F(1,29) = 14.2$, $p = .001$.

S-R interference. For the magnitude of the interference on RTs (see Figure 2.4b), the mixed ANOVA (Interference × Age) revealed an effect of the type of interference, $F(2,84) = 142.7$, $p < .001$, $\varepsilon = .875$, as the interference on RTs was greater when position was incompatible with the response than when it was not (CDIP > IDCP, $p = .001$; IDIP > IDCP, $p < .001$). The Interference × Age interaction was significant, $F(4,84) = 6.7$, $p < .001$, $\varepsilon = .875$, although pairwise comparisons revealed the same task effects for all age groups—CDIP > IDCP: young ($p < .001$), middle-aged ($p < .001$), and elderly ($p < .001$); IDIP > IDCP: young ($p = .046$), middle-aged ($p < .001$), and elderly ($p < .001$).

The distributional analysis (Figure 3) revealed the following effects:

In young adults, IDCP interference was significant in QIP1, $t(14) = 3.6$, $p = .003$, QIP2, $t(14) = 3.1$, $p = .007$, and QIP3, $t(14) = 3.5$, $p = .004$; CDIP interference was significant in QIP1, $t(14) = 9.3$, $p < .001$, QIP2, $t(14) = 7.1$, $p < .001$, QIP3, $t(14) = 7.1$, $p < .001$, and QIP4, $t(14) = 4.8$, $p < .001$; and IDIP interference was significant in QIP1, $t(14) = 6.3$, $p < .001$, QIP2, $t(14) = 6.2$, $p < .001$, QIP3, $t(14) = 7.3$, $p < .001$, and QIP4, $t(14) = 5.5$, $p < .001$.

In middle-aged adults, IDCP interference was significant in QIP3, $t(14) = 3.0$, $p = .009$, and QIP4, $t(14) = 2.5$, $p = .024$; CDIP interference was significant in QIP1, $t(14) = 7.6$, $p < .001$, QIP2, $t(14) = 9.4$, $p < .001$, QIP3, $t(14) = 7.3$, $p < .001$, and QIP4, $t(14) = 4.0$, $p = .001$; and IDIP interference was significant in QIP1, $t(14) = 8.7$, $p < .001$, QIP2, $t(14) = 7.7$, $p < .001$, QIP3, $t(14) = 8.1$, $p < .001$, and QIP4, $t(14) = 2.9$, $p = .001$.

In elderly adults, CDIP interference was significant in QIP1, $t(14) = 13.1$, $p < .001$, QIP2, $t(14) = 14.1$, $p < .001$, QIP3, $t(14) = 12.8$, $p < .001$, and QIP4, $t(14) = 6.2$, $p < .001$; and IDIP interference was significant in QIP1, $t(14) = 10.7$, $p < .001$, QIP2, $t(14) = 8.9$, $p < .001$, QIP3, $t(14) = 5.0$, $p < .001$, and QIP4, $t(14) = 5.0$, $p < .001$.

For the PE (see Table 2), the mixed ANOVA (Position × Direction × Age) revealed a significant effect of the position, $F(1,42) = 41.5$, $p < .001$, as the PE was greater in trials with incompatible position than with compatible position

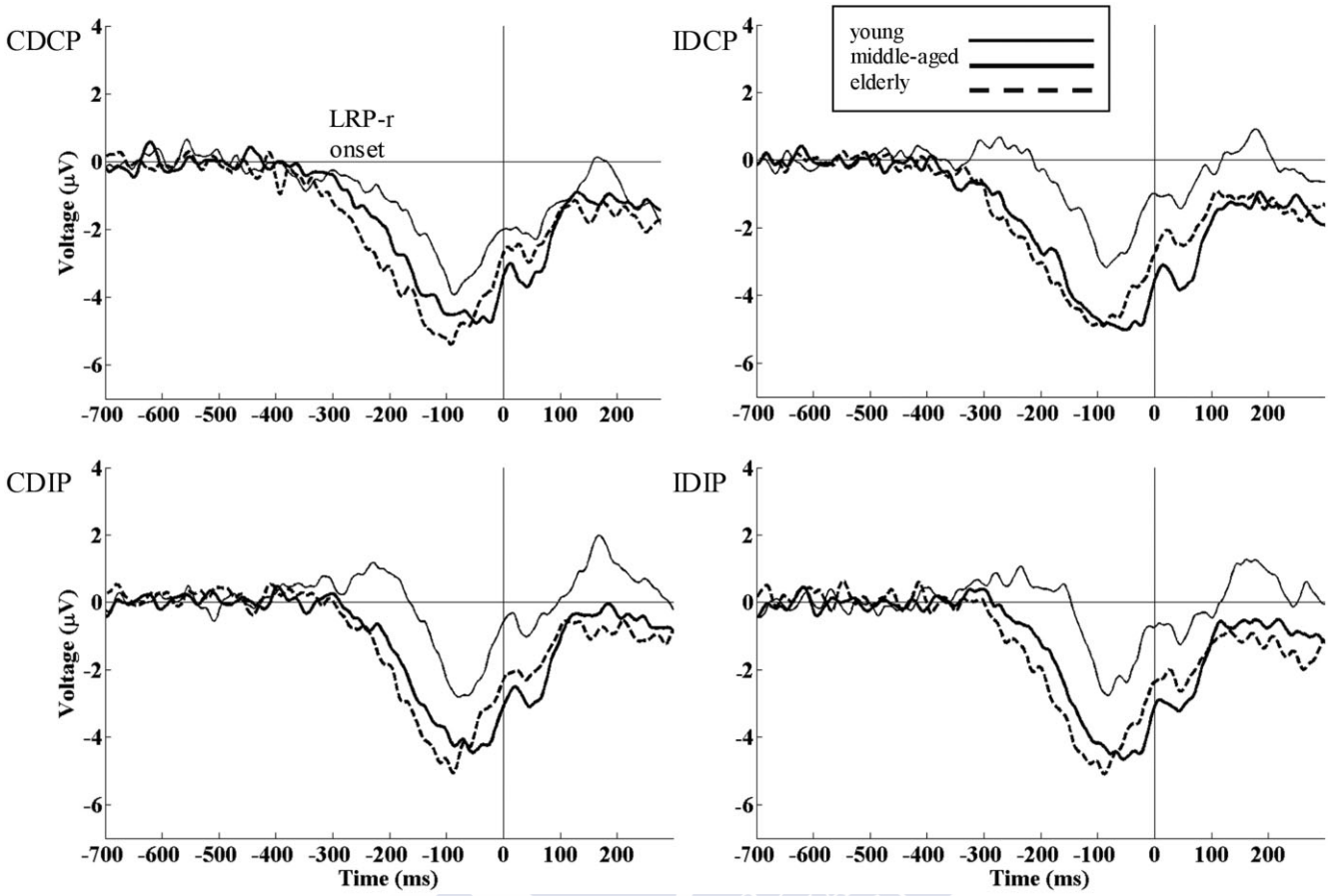

Figure 4. Response-locked lateralized readiness potential (LRP-r) for the three groups: young (gray solid waveform), middle-aged (black solid waveform), and elderly (black dashed waveform) in the four conditions (CDCP, IDCP, CDIP, and IDIP). The LRP-r onset latency was recorded (as the point where the negative trend in the waveform begins). The LRP-r onset was earlier in middle-aged and elderly than in young participants, as indicated by longer time for response execution in middle-aged and elderly than in young participants. The LRP-r onset was also earlier in elderly than in middle-aged participants, indicating prolonged response execution in elderly relative to the middle-aged participants.

($p < .001$). Direction also had a significant effect, $F(1,42) = 4.9$, $p = .033$, as the PE was greater when the direction was incompatible than when it was compatible with the response to the color ($p = .033$). Position × Direction × Age showed a significant interaction effect, $F(2,42) = 3.6$, $p = .035$. In young adults, the PE was greater when position was incompatible than when it was compatible, regardless of whether direction was compatible (CDIP > CDCP) ($p = .002$) or incompatible with the response (IDIP > IDCP) ($p < .001$), whereas a direction effect was only observed when position was incompatible with the response, that is, IDIP > CDCP ($p = .007$). On the other hand, in the middle-aged group, when the stimulus position was compatible, the PE was greater when the direction was incompatible than when it was compatible ($p = .038$) (IDCP > CDCP). In elderly adults, there were no differences between conditions in the PE.

ERPs

Slowing. For the onset latency of the LRP-r (see Table 2, Figure 4, and Figure 2.2b), the mixed ANOVA (Position × Direction × Age) revealed a significant effect of the factor age, $F(2,42) = 17.7$, $p < .001$, as earlier LRP-r onset was observed in elderly than in middle-aged ($p = .022$) and young participants ($p < .001$) and in middle-aged than in young participants ($p = .009$). Position also exerted an effect, $F(1,42) = 113.1$, $p < .001$, as the LRP-r onset was earlier when the position was compatible than when it was incompatible with the response ($p < .001$). The ANOVA also revealed a significant effect of the interaction Direction × Age, $F(1,42) = 3.33$, $p = .046$. In young adults only, the LRP-r onset was earlier when the direction was compatible than when it was incompatible ($p = .001$).

For the LRP-s peak latency (see Table 2 and Figure 5), the mixed ANOVA (Position × Direction × Age) revealed an effect of the age, $F(2,42) = 14.5$, $p < .001$, as LRP-s latencies were longer in elderly participants than in middle-aged ($p = .050$) and young ($p < .001$) participants. LRP-s latencies were also longer in middle-aged participants than in young participants ($p = .018$). Position had a significant effect, $F(1,42) = 62.0$, $p < .001$, as LRP-s latencies were delayed when the position was incompatible than when it was compatible with the response ($p < .001$). The ANOVA also revealed a Direction × Age interaction effect, $F(2,42) = 5.05$, $p = .011$. In young adults only, the LRP-s peak latency was longer when the direction was incompatible than when it was compatible ($p < .001$).

For the LRP-s amplitude, the mixed ANOVA (Position × Direction × Age) revealed an effect of the age,

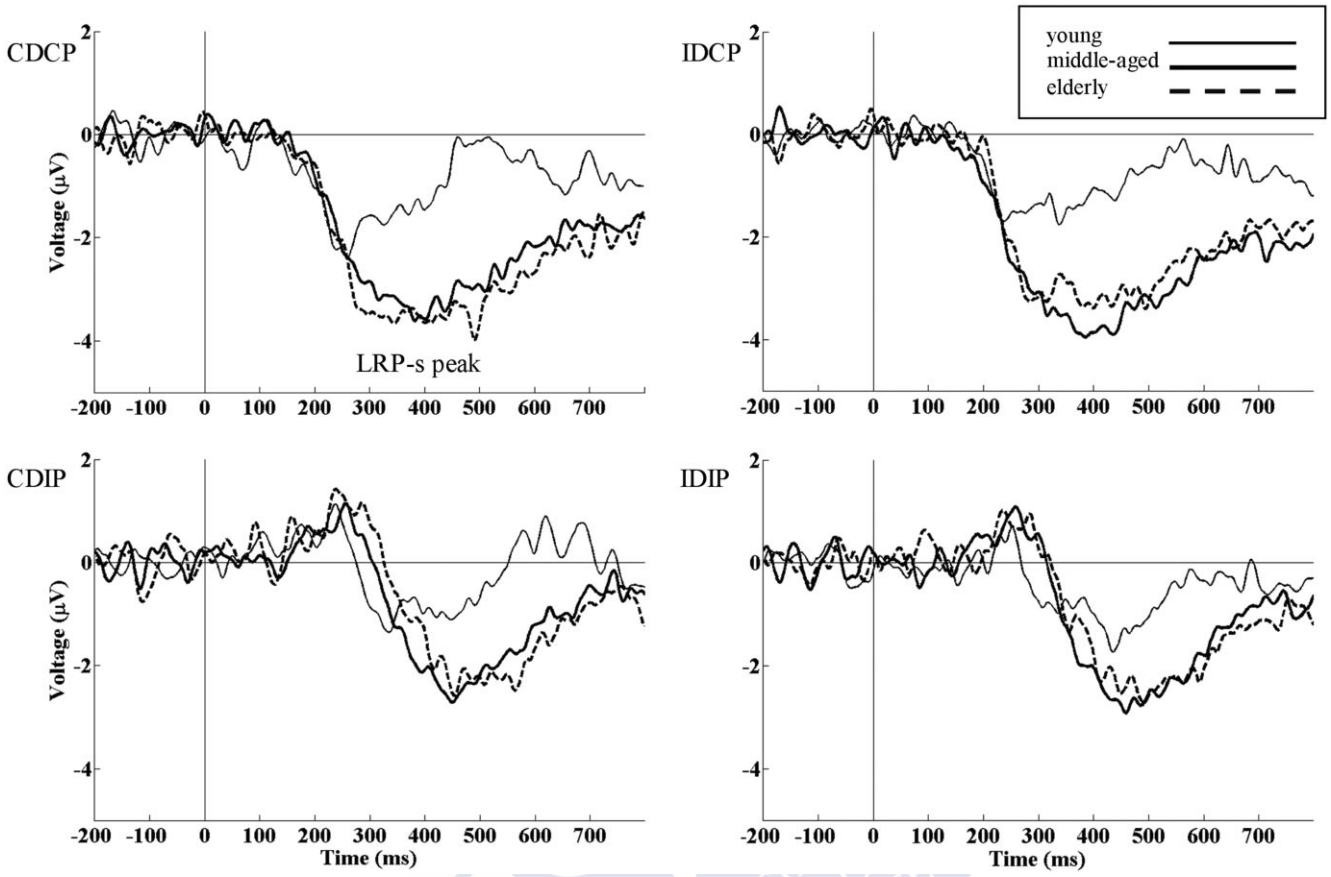

Figure 5. Stimulus-locked lateralized readiness potential (LRP-s) at the C3/C4 electrode pair for the three groups: young (gray solid waveform), middle-aged (black solid waveform), and elderly (black dashed waveform) in the four conditions (CDCP, IDCP, CDIP, and IDIP). LRP-s latency (300–650 ms) was slower in conditions in which behavioral interference was observed. The LRP-s latency also slowed with aging in accordance with behavioral data.

$F(2,42) = 7.94$, $p < .001$, as the LRP-s amplitude was larger in elderly than in young ($p = .010$) adults, and it was larger in middle-aged than in young ($p = .002$) participants. Position also had a significant effect, $F(1,42) = 5.84$, $p = .020$, as the LRP-s amplitude was larger when the position was compatible than when it was incompatible with the response.

For the N2pc peak latency (see Table 2, Figure 6, and Figure 2.1b), the mixed ANOVA (Position × Direction × Age) revealed an effect of age, $F(2,42) = 41.4$, $p < .001$, as the N2pc peak latency was shorter in young than in middle-aged participants ($p < .001$), and it was shorter in young than in elderly participants ($p < .001$). The mixed ANOVA (Position × Direction × Age) conducted for the N2pc onset did not reveal any significant effect.

Linear regression between LRP-r onset latency and age of the participants (middle-aged and elderly) showed a significant linear trend in CDCP: $R^2 = .346$, $F(1,29) = 14.8.6$, $p = .001$; IDCP: $R^2 = .165$, $F(1,29) = 5.5$, $p = .26$; CDIP: $R^2 = .173$, $F(1,29) = 5.8$, $p = .022$; and IDIP: $R^2 = .353$, $F(1,29) = 15.3$, $p = .001$. The average LRP-r values among the conditions also revealed a significant linear trend, $R^2 = .310$, $F(1,29 = 12.6$, $p = .001$ (see Figure 7). No linear relationships between N2pc peak latency and age of the participants were found (see Figure 7).

The correlations between LRP-r onset latency and RT were significant in the four conditions: CDCP ($r = .51$, $p = .004$), IDCP ($r = .45$, $p = .013$), CDIP ($r = .68$, $p < .001$), and IDIP ($r = .70$, $p < .001$). The correlation between the average RT and LRP-r onset latency values among the conditions was significant ($r = .67$, $p < .001$). Correlation analyses between RT and N2pc peak latency did not reveal any significant effects.

S-R interference. The mixed ANOVA (Condition × Age), carried out to study age-related differences in delays of the preparation of the correct response onset, revealed an effect of the condition, $F(2,84) = 31.52$, $p < .001$, $\varepsilon = .786$, as the LRP-r onset was less delayed in IDCP than in CDIP and IDIP ($p < .001$). The age factor was not significant.

The positive dip observed in LRP-r (Figure 4) was statistically significant for the young participants in those conditions where the interference was manifested—IDCP: $t1(14) = 2.6$, $p = .019$; $t2(14) = 2.9$, $p = .011$; $t3(14) = 3.1$, $p = .008$; $t4(14) = 3.0$, $p = .010$; $t5(14) = 2.3$, $p = .040$; CDIP: $t1(14) = 6.9$, $p < .001$; $t2(14) = 6.7$, $p < .001$; $t3(14) = 5.7$, $p < .001$; $t4(14) = 4.4$, $p < .001$; $t5(14) = 3.5$, $p = .040$; and IDIP: $t1(14) = 6.0$, $p < .001$; $t2(14) = 6.6$, $p < .001$; $t3(14) = 6.8$, $p < .001$; $t4(14) = 6.0$, $p < .001$; $t5(14) = 4.3$, $p = .001$ conditions.

Perceptual conflict. For the N2pc amplitude (see Figure 6 and Figure 2.3b), which indicates the amount of attentional resources allocated to a target, the mixed ANOVA (Position × Direction × Age) revealed an effect of the Position ×

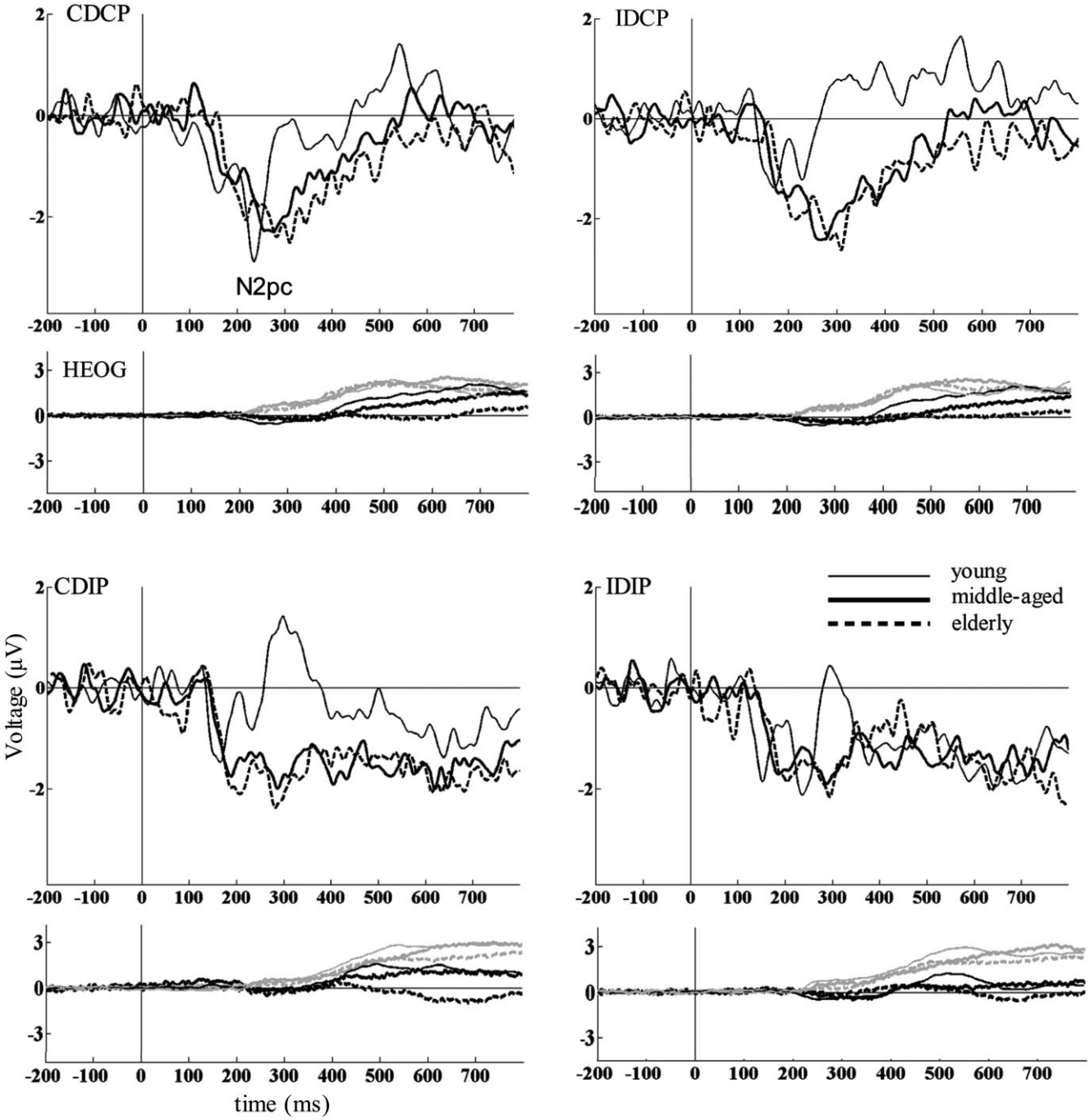

Figure 6. Negativity posterior contralateral (N2pc) at the PO7/PO8 electrode pair for the three groups: young (gray solid waveform), middle-aged (black solid waveform), and elderly (black dashed waveform) in the four conditions (CDCP, IDCP, CDIP, and IDIP). The N2pc peak latency was longer in middle-aged and elderly than in young participants, indicating that the electrophysiological activity associated with visuospatial processing of the target stimulus was delayed in middle-aged and elderly relative to young participants. There were no differences in N2pc latency between middle-aged and elderly participants. In young participants, the N2pc amplitude was smaller in IDCP/CDIP than in CDCP/IDIP, which suggests interference in processing stimuli with conflicting spatial information. HEOG was also graphically represented (light waveforms: right side ocular movements; dark waveforms: left side ocular movements).

Direction × Age, $F(2,42) = 4.19$, $p = .022$, as differences among conditions were only observed in young adults. Specifically, N2pc amplitudes were larger in young participants when the direction and position conveyed the same information as when they conveyed the opposite information (CDCP > CDIP, $p = .001$; CDCP > IDCP, $p < .001$; IDIP > CDIP, $p = .039$; IDIP > IDCP, $p = .041$). Also, when the position was compatible and the direction incompatible (i.e., in IDCP), the N2pc amplitude was smaller in young participants than in middle-aged ($p = .054$) and elderly ($p = .042$) participants.

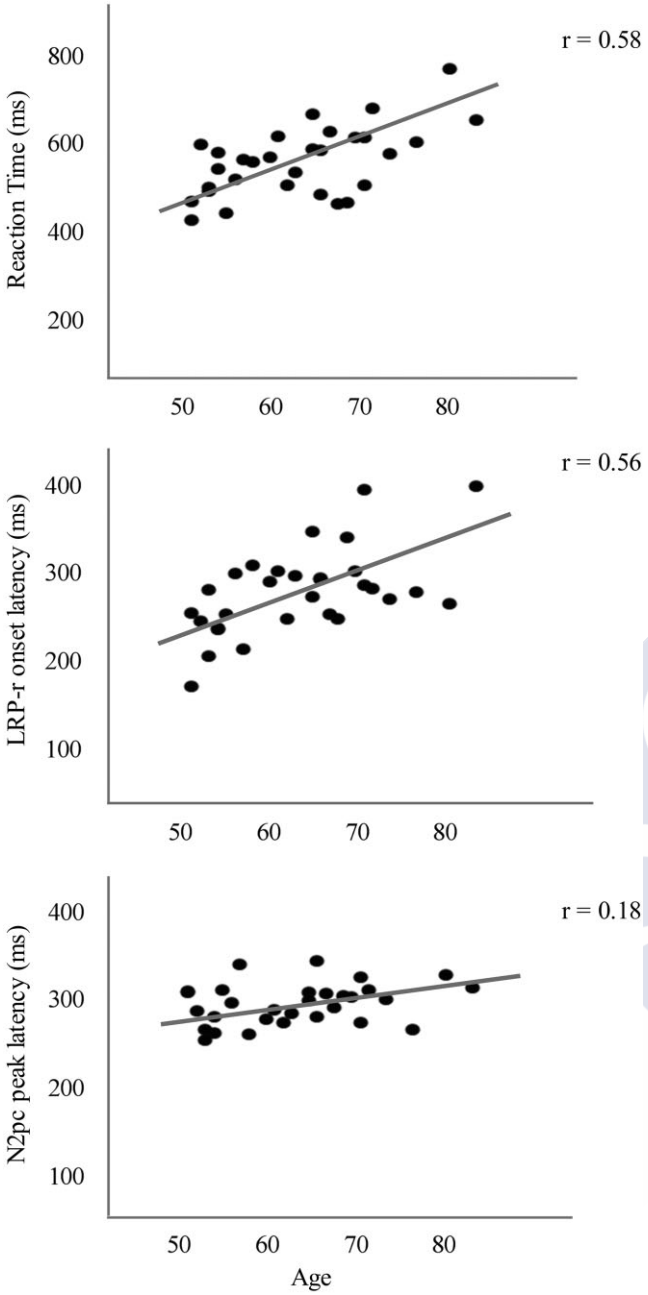

Figure 7. Scatter plots and regression lines for RT (top), LRP-r (middle), and N2pc (bottom) values on the age of each participant in the middle-aged and elderly groups. The corresponding coefficient of correlation between years of age and, respectively, RT, LRP-r, and N2pc is shown at the top right-hand side of each graph.

Discussion

The overall aim of the present study was to shed light on the modulation of ERP correlates of motor execution (LRP-r) and visuospatial processing (N2pc) in a sample of young, middle-aged, and elderly participants who performed an SRC task. The results revealed the following: (a) age-related slowing in RTs; (b) progressive slowing with age in the response execution stage (LRP-r onset) and similar slowing in visuospatial processes (N2pc peak) in middle-aged and elderly relative to young participants; (c) similar position interference in the three age groups and direction interference only in the young group (and also in middle-aged for slower responses); (d) increased LRP amplitudes in the older groups relative to young participants; (e) perceptual conflict by contradictory spatial information, conveyed by the irrelevant dimensions, only in young participants (smaller N2pc amplitude in IDCP and CDIP than in CDCP and IDIP).

An age-related slowing of the RT was observed (longer RT in the elderly than in the middle-aged and young, and longer RT in the middle-aged than in the young participants). Those results are consistent with the age-related slowing in the performance of a Simon task demonstrated in previous studies (Castel, Balota, Hutchison, Logan, & Yap, 2007; Juncos-Rabadán et al., 2008; Proctor, Vu, & Pick, 2005; Van der Lubbe & Verleger, 2002). Therefore, the data from the present study support the well-known report of age-related slowing in the speed of response (Salthouse, 2009). Importantly, ERP correlates provided evidence about differences in the pattern of slowing in each particular process, which supported the concept of heterogeneity of the cognitive processes in the pattern of slowing (Park et al., 2002).

The LRP-r onset, an ERP correlate of the motor execution of the response, revealed a gradual slowing in the motor execution stage; that is, the slowing was greater in middle-aged and elderly relative to the young group, and it was also greater in elderly than in middle-aged participants. These results are consistent with the findings of previous studies (Falkenstein et al., 2006; Kolev et al., 2006; Roggeveen et al., 2007; Wild-Wall et al., 2008; Yordanova et al., 2004) and with the suggestion that the motor response execution stage represents a main source of the age-related slowing observed in RTs (Falkenstein et al., 2006; Kolev et al., 2006), which is also supported by the correlation between RT and duration of the response execution stage.

The results also showed that execution of the motor response represents a locus of age-related slowing that is already manifested in the middle-aged participants and that is further increased in the elderly participants, as also revealed by the linear regression analyses (see Figure 7, middle plot). Thus, the slower execution of the response may explain the slowing observed in RT in the elderly and middle-aged groups with respect to the young group, as well as the slowing in RT for the elderly group relative to the middle-aged group.

On the other hand, the N2pc onset did not show differences with age. However, the N2pc peak latency was slower in middle-aged and elderly than in young participants. These results are consistent with the results of Van der Lubbe and Verleger (2002) and suggest that age-related slowing did not occur at the moment when attentional shift starts (N2pc onset), but at the time when the discrimination of the target stimulus is most pronounced (N2pc peak latency). The age-related slowing in N2pc peak latency was also consistent with results of visual search tasks (Amenedo et al., 2012; Lorenzo-López et al., 2008, 2011). Therefore, these results suggest that, in the Simon task, processes associated with visuospatial processing of the target stimulus slow down in healthy elderly and also in middle-aged participants compared to young participants, contributing to the slowing observed in RT in the two older groups. However, and consistent with linear regression and correlation analyses, slowing in the latencies of response in elderly relative to middle-aged participants may be explained by delays in response-related processes but not by delays in visuospatial processes.

It cannot be entirely excluded that N2pc was shortened in young participants due to the positive wave observed after 250 ms. This

positive wave may be related with the temporal contralateral component, which was involved in isolating the target once it was already identified (see Hilimire, Mounts, Parks, & Corballis, 2009, 2010). Therefore, it would represent a later process. Importantly, the observed age-related differences in N2pc latency are consistent with the results obtained by Van der Lubbe and Verleger (2002) with a similar task. In addition, the present results show that the N2pc latency was not delayed in elderly relative to middle-aged participants, and it can be reliably stated since the above positivity was not present in any of the older groups.

The present results support the existence of different patterns of age-related changes for each particular process, which is consistent with the notion of heterogeneity of the cognitive functions in the pattern of age-related decline (Park et al., 2002). In fact, onset of attentional shift to the target stimulus was preserved. However, the time at which attentional shift to the target stimulus is most pronounced was delayed in middle-aged and elderly relative to young participants, whereas there were no differences between the older adult groups. The response execution stage was also gradually slowed with age, although, in contrast to the pattern of decline in discrete stages suggested by studies on fluid cognitive skills (Finkel et al., 2003; McArdle et al., 2002; Willis & Schaie, 2005), the results of the linear regression analysis suggest a gradual slowing from 50 years of age, up to 84 years.

Regarding the interference effect, the RT was shorter and the PE was higher when the stimulus position was incompatible with the response, which was consistent with previous findings in young (Lu & Proctor, 1995) and elderly (Proctor, Vu, & Pick, 2005) participants. However, age-related increase in interference was not observed, which is not consistent with the findings of previous studies (Bialystok et al., 2004; Castel et al., 2007; Juncos-Rabadán et al., 2008; Proctor, Vu, & Pick, 2005; Van der Lubbe & Verleger, 2002) that supported the inhibitory deficit hypothesis (Hasher & Zacks, 1988; Zacks & Hasher, 1997). Nonetheless, evidence for an absence of age-related differences on the Simon effect has previously been reported (Kubo-Kawai & Kawai, 2010; Proctor, Pick, Vu, & Anderson, 2005) and was attributed to the experimental design.

In the present study, the absence of increased interference with age may be related to age-related differences in the effect of direction. Specifically, the direction of the arrow interfered in the responses of young participants (slower RT and greater PE in the IDCP than in the CDCP condition), which is consistent with previous findings (Masaki, Takasawa, & Yamazaki, 2000; Wittfoth, Schardt, Fahle, & Herrmann, 2009); however, it affected slower responses only in middle-aged participants, and the effect was totally absent in elderly participants. If the direction of the arrow does not produce interference in the task used in the present study, then position-direction interaction (in IDIP) is probably absent as well as the perceptual conflict conveyed by contradictory spatial information (in IDCP and CDIP conditions). Therefore, interference in the three incompatible conditions is attenuated in the older groups.

Stimulus position is known to attract attentional resources more quickly than the direction of the stimulus (Klein & Ivanoff, 2011). This has been attributed to mandatory semantic processing of the direction (Iani, Baroni, Pellicano, & Nicoletti, 2011; Symes, Ellis, & Tucker, 2005; Vainio, Ellis, & Tucker, 2007). In accordance with the model of the temporal overlap (see Hommel, 2000), if an irrelevant dimension is processed after the response, then it does not affect the performance. In the present study, the distributional analysis showed that the direction interfered throughout the distribution of RTs in young participants (i.e., from shorter to longer RTs). However, the direction only interfered in slower responses in middle-aged participants, and it did not interfere in elderly participants. Thus, on the basis of the distributional analysis, it may be hypothesized that aging affects the speed of processing of the arrow direction (due to its symbolic nature) more than it affects processing of the arrow position and color. This interpretation is also consistent with greater age-related decline in effortful than in automatic processes (Hasher & Zacks, 1979).

ERP correlates of interference in response-related processes (LRP) and perceptual conflict in allocating attention to the target stimulus (N2pc) provided additional information.

The interference from the stimulus position similarly affected the motor execution stage, delaying LRP-r onset in the three age groups, which was consistent with similar levels of behavioral interference. Interference in the response execution stage by stimulus position was consistent with previous findings (Vallesi, Mapelli, Schiff, Amodio, & Umiltà, 2005). In addition, the incompatibility of the arrow direction also delayed the LRP-r onset, which is consistent with behavioral data and with a previous study in a sample of young participants (Masaki et al., 2000). Moreover, the LRP-s latency was delayed when interference was manifested (i.e., in IDCP, CDIP, IDIP for the young; in CDIP/IDIP for the older groups) and, consistently with RTs, an age-related slowing in LRP-s latency was observed.

The amplitude of LRP-s was greater in middle-aged and elderly participants than in the young group. Similar results were reported in previous studies (Roggeveen et al., 2007; Wild-Wall et al., 2008; Yordanova et al., 2004), in which the increased LRP amplitudes were associated with declined inhibitory control (Roggeveen et al., 2007) and dysregulation in high-level control systems (Wild-Wall et al., 2008). In the present study, increased LRP amplitudes were not accompanied by increased interference. Therefore, on the basis of the compensation hypothesis (Reuter-Lorenz & Cappell, 2008), the present results suggest that larger LRP amplitudes may be related to additional mechanisms recruited for maintaining the performance.

Age-related differences in the shape of the LRP-r waveform were also observed. Specifically, the young participants showed a positive dip related to transitory preparation of the incorrect response in all the conditions in which S-R incompatibility was present (i.e., IDCP, CDIP, and IDIP). However, this positive wave was not present in the older groups, possibly because of delayed activation of the automatic response based on the position in the older groups, in accordance with the possible delay in the incorrect preparation/N2cc complex observed for the CDIP and IDIP conditions in LRP-s waveforms. However, future studies are required to test this hypothesis since incorrect preparation and N2cc could not be isolated under the present experimental design.

The direction of the arrow elicited an effect of interference only in young participants. This may explain why ERP evidence of a perceptual conflict related to contradictory spatial information conveyed by both irrelevant dimensions was obtained only in young participants. In the IDCP and CDIP conditions, the arrow was on the opposite side with respect to where it was indicating. In these conditions, the N2pc amplitudes were smaller in the young but not in the older participants, relative to the CDCP/IDIP conditions. This effect suggests that the contradictory information reduced the amount of attentional resources devoted to the target stimulus. This finding is consistent with data obtained by Cespón et al. (2013) in a sample of young participants and with N2pc modulations

generated by high-level properties of the display (Eimer & Kiss, 2007; Telling, Kumar, Meyer, & Humphreys, 2009). Nonetheless, it must to be noted that perceptual conflict is always accompanied by S-R incompatibility (from the direction of the arrow in IDCP and from the arrow position in CDIP), which constitutes a limitation of the present experimental design.

The N2pc amplitude was larger in middle-aged and elderly groups than in the young group, for the IDCP condition. These differences may also be related to the contradictory information conveyed by both irrelevant features, which reduced the N2pc amplitude in young but not in middle-aged and elderly participants. Moreover, studies involving visual search tasks found smaller N2pc in elderly than in young participants (Amenedo et al., 2012; Lorenzo-López et al., 2008, 2011; but see also Lien, Gemperle, & Ruthruff, 2011), which was related to differences in activity to suppress the distractor stimuli. Experimental manipulations have linked the N2pc with processing of the target as well as suppression of the distractor/s (Hickey et al., 2009). Thus, in the present study, nontarget suppression-related activity, which occurs when various stimuli that fall within the same receptive field compete for cortical representation (Luck, Girelli, McDermott, & Ford, 1997), cannot be entirely excluded. However, considering that in the present study target and nontarget appeared in opposite hemifields and separated by 7.5°, it is possible that N2pc basically reflects activity related to target processing. Importantly, differences between age-related modulations of target processing and distractor suppression might be found. Future studies could be specifically designed to explore this possibility.

In summary, the results of the present study using an SRC task showed an age-related slowing in RT. Importantly, the ERP results provided support for the heterogeneity in the patterns of cognitive slowing on each particular process. In fact, although the onset of the attentional shift to the target stimulus (N2pc onset) was preserved with age, the time when that attentional shift is more pronounced (N2pc peak) was delayed in middle-aged and elderly participants relative to the younger group. By contrast, execution of the response (LRP-r) gradually slowed with increasing age. Moreover, although no evidence for declined inhibitory control was found, increased LRP amplitudes suggested compensatory mechanisms to maintain performance. The lack of differences in interference was related to greater masking of the direction effect by the stimulus position in the older groups. Also, only the younger participants were affected by the perceptual conflict due to the contradictory spatial information conveyed by both irrelevant dimensions in IDCP and CDIP conditions, as revealed by modulations in the N2pc amplitude.

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2.5 Study 5 (Estudio 5)

Cespón, J., Galdo-Álvarez, S., & Díaz, F. (under review, b). Electrophysiological correlates of amnestic mild cognitive impairment in a Simon task. *PLOS ONE*.

El deterioro cognitivo ligero amnésico (DCLa) representa un estadio prodrómico de la enfermedad de Alzheimer –EA- (Petersen et al., 2009). Por lo tanto, sería importante disponer de biomarcadores de DCLa con objeto de instaurar intervenciones tempranas que ayuden a enlentecer la progresión hacia la EA. Los potenciales evocados (PE) proporcionan medidas no invasivas y de bajo coste para el estudio electrofisiológico de los procesos cognitivos. Considerando estas características, los biomarcadores obtenidos con PE son interesantes desde un punto de vista clínico. En el presente estudio, la actividad EEG fue registrada en 25 adultos sanos y 27 participantes diagnosticados de DCLa mientras ejecutaban una tarea Simon (tarea CER-pd). Se estudiaron los PE asociados con procesos visoespaciales (N2 posterior contralateral, N2pc) y motores (Potencial de preparación lateralizado, PPL). La amplitud de N2pc fue menor en pacientes con DCLa que en adultos sanos, lo que sugiere la existencia de un déficit asociado al DCLa en la asignación de recursos atencionales al estímulo target. Del mismo modo, la amplitud del PPL fue menor en los pacientes con DCLa que en los participantes sanos, revelando así una reducción en los recursos motores disponibles para ejecutar la respuesta en los participantes diagnosticados de DCLa. Además, la amplitud del PPL mostró ser un buen biomarcador de DCLa, ya que en las curvas ROC, el área bajo la curva fue de 0.86. Eligiendo como punto de corte 3.75 μV, la sensibilidad fue de 0.85 y la especificidad de 0.92.

Title: Electrophysiological correlates of amnestic mild cognitive impairment in a Simon task.

Short title: amnestic mild cognitive impairment correlates

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ABSTRACT

Amnestic mild cognitive impairment (aMCI) represents a prodromal stage of Alzheimer`s disease (AD) (Petersen et al., 2009). Thus, aMCI biomarkers are important for enabling early interventions to help slow down progression of the disease. Recording event-related potentials (ERPs) is a non-invasive and inexpensive measure of brain activity of cognitive processes, and it is of interest from a clinical point of view. In the present study, EEG activity was recorded in 25 healthy participants and 27 aMCI patients while they performed a Simon task. The ERPs associated with visuospatial (N2 posterior-contralateral (N2pc) and motor (lateralized readiness potential (LRP) processes were examined. The N2pc amplitude was smaller in patients with aMCI than in healthy participants, which indicated a decline in the allocation of attentional resources to the target stimulus. Likewise, the LRP amplitude was smaller in aMCI patients than in healthy participants, which revealed a reduction in the motor resources available to execute the response in the aMCI patients. Furthermore, the LRP amplitude proved to be a valid biomarker (0.85 sensitivity, 0.92 specificity) of aMCI.

Introduction

The pathophysiological processes involved in Alzheimer's disease (AD) are thought to take place before development of dementia [1]. However, clinical diagnosis of AD is usually made once a patient has developed impairment in multiple cognitive domains that are sufficient to interfere with social routine and/or occupational function.

Mild Cognitive Impairment (MCI) is diagnosed when symptoms suggestive of AD are present but they are not sufficient to interfere in lifestyle [2,3]. Neuropathological [4] and electroencephalographic (EEG) data [5] support the hypothesis that MCI may represent a preclinical stage of AD [6]. Indeed, it has been shown that a high percentage of MCI patients develop dementia within a few years [7]. Thus, MCI markers would constitute good indicators for early treatment [6], which should slow down the progression of the disease [8].

Several studies have highlighted the existence of valid biomarkers of the MCI state [6,9], but such biomarkers are expensive (fMRI) and invasive (e.g. positron emission tomography (PET) and cerebrospinal fluid measures). On the contrary, recording EEG and event-related potentials (ERPs) is a suitable method for obtaining MCI biomarkers, since it is a widely diffused, non-invasive and relatively inexpensive procedure [10]. In addition, temporal resolution of the ERPs is also especially useful for addressing the speed of the cognitive processes in order to establish differences in brain electrical measures between MCI and normal ageing.

The study of ERP correlates of some cognitive processes might be of particular interest for distinguishing MCI patients from healthy participants on the basis of brain electrical activity. Evidence has been obtained regarding the early impairment of spatial and attentional processes in the progression from normal ageing to AD [11]. In addition, the progressive slowing of reaction time (RT) with increasing age has been attributed to

slowing of the motor generating system [12]. Considering that RT is usually longer at very early stages of AD [13], ERP correlates of motor processes may be sensitive to the MCI state.

The posterior contralateral negativity (N2pc) is an ERP component that is related to visuospatial processing of a target stimulus. N2pc appears contralaterally to the visual hemifield in which the target is located, 200-300 ms after the onset of a bilateral stimuli array [14-17]. The N2pc latency has proved to be a reliable measure of the attentional shift to possible targets [17,18], whereas the N2pc amplitude reflects the amount of attention that is allocated to a stimulus [19].

Previous studies have shown an age-related slowing in the allocation of attentional resources to the target stimulus (revealed by a longer N2pc latency) in visual search tasks [20,21] as well as Simon tasks [22]. The N2pc amplitude was also smaller in elderly than in younger participants during visual search tasks [20,21] although no differences were found in another study [23]. As concluded in the review by Iachini et al (2009) [11], attentional and spatial deficits are expected to appear at very early stages of dementia, so that evaluation of visuospatial processes is considered as a promising approach in the search for predictive markers of AD. However, as far as we know, no previous studies have evaluated the N2pc activity in MCI patients.

The age-related slowing in motor processes was mainly located at the response execution stage, as revealed by studies examining the response-locked lateralized readiness potential (LRP-r) [24-28]. Considering a possible slowing in RT in MCI patients in comparison to healthy elderly, along with impairment in primary motor regions [29], MCI-related changes in response execution stage should be investigated. Moreover, larger LRP amplitudes were observed in healthy older participants than in young participants [24,25,27], which suggests a higher activation threshold of the motor

cortex to execute the response in elderly participants. In this context, larger LRP amplitudes were related to less successful inhibitory control [26,30]. Given that MCI patients showed decreased inhibitory control in several studies [31,32], differences in LRP amplitude between aMCI patients and healthy participants may be expected.

In the present study, EEG activity was recorded while participants performed a Simon task. In Simon tasks, participants respond to a non spatial feature of a lateralized stimulus while they have to ignore the stimulus position (for reviews on the Simon task, see 33, 34]. This paradigm enables study of the visuospatial processing of the lateralized stimulus as well as response-related processes. The aim of the present study was to explore differences in brain electrical activity between healthy participants and amnestic MCI (aMCI) patients, in order to obtain possible ERP markers of the aMCI state. Therefore, the present study focused on N2pc and LRP-r components.

Deficits in spatial abilities are expected to appear at very early stages in the progression from normal ageing to AD. Consequently, we expected to find differences in the N2pc component between healthy and aMCI participants. Specifically, delays in N2pc latency and/or reductions in N2pc amplitude (related to delayed and reduced allocation of attentional resources to the processing of the target stimulus respectively) were expected in aMCI patients, relative to healthy participants.

Regarding motor processes, a lengthening of the response execution stage in aMCI patients relative to healthy participants was expected, which would be indicated by earlier LRP-r onset in aMCI patients than in healthy elderly. Also, differences between healthy participants and aMCI participants might be found in LRP amplitudes as a consequence of deficits in inhibitory control.

Method

Participants

Fifty-two participants (25 women, 27 men) between 51 and 84 years of age (mean age 66.8 years) were recruited from the general population. The participants were divided into 2 groups according to Diagnosis: Control Group (CG (25 participants: 11 women, 14 men), Age Mean: 65.0 (SD: 8.1)) and amnestic MCI group (aMCI (27 participants; 14 women, 13 men), Age Mean: 68.4 (SD: 8.8)). The participants volunteered to take part in the study, which received prior approval by the local ethical review board. All the participants were right-handed (evaluated by the Edinburgh Handedness Inventory [35]). All participants had normal or corrected to normal vision, and none had any history of neurological or psychiatric disorders. Also, the study was approved by the USC ethics committee and by the Galicia Clinical Research ethics committee. The participants received an informative protocol where they were informed on the aims of the research. Also, we explained to the participants the procedure and the type of tasks to carry out in the neuropsychological and EEG sessions as well as the purposes of the study. When the participants came accompanied by a relative, both were present in the moment of explaining the tasks to perform as well as the aims of the research. All participants gave written informed consent prior to their inclusion in the study. All participants had ethical and legal ability for signing the written informed consent because those participants with signs and/or symptons of dementia were excluded of the present research. All potential participants who declined to participate were not disadvantaged in any other way by not participating in the study.

All of the MCI patients were amnestic MCI patients (aMCI), as these patients are more likely to develop AD dementia [6]. MCI participants fit the diagnostic criteria proposed by Petersen et al (1999) [3]: subjective memory complaints; objectified

memory impairment; absence of impairment in daily activities; absence of diagnosis criteria for dementia. The following tests were used to diagnose aMCI: an adapted version [36] of the Mini-mental state Examination (MMSE) [37]; an adapted version [38] of the California Verbal Learning Test [39]; the Cambridge examination for mental disorders in elderly (CAMDEX-r) [40]; a questionnaire on subjective memory complaints [41]; the instrumental activities of daily living scale (IADL) [42]; and the Geriatric depression scale (GDS) [43]. Participants also completed a questionnaire with socio-demographic and clinical data. Finally, there were no differences regarding years old and years of schooling based on the diagnosis.

Task

A series of red or blue arrows pointing either left or right was displayed on a screen against a black background. The screen was placed 100 cm in front of the participants. The arrow stimuli subtended 2.87º long and 1.72º wide of the visual field. The visual angle between the central cross on the screen and the internal edge of the arrow was 2.29º, and the visual angle between the cross and the external edge of the arrow was 5.16º, so the entire stimulus was presented in the parafoveal region [44]. A grey geometric figure of similar morphology and eccentric position (two orthogonally superimposed bars, the vertical thicker than the horizontal, see Figure 1) was presented in the opposite hemifield to the target with the aim of preventing exogenous lateralization in the electroencephalogram (EEG). The arrows (and the contralateral geometric figure) were presented for 125 ms, with 2000 ms inter-trial intervals. The participants were instructed to direct their gaze towards the central cross throughout the task; this, along with the short interval during which the stimuli were presented, minimized the likelihood of ocular movements towards the area where the arrow appeared [45].

Procedure

Participants carried out the task while seated in a comfortable chair in a dimly lit, sound-attenuated, electrically shielded chamber. They were instructed to respond to the colour of a blue or red arrow by pressing one of two horizontally positioned buttons (blue or red), but to ignore the position and the direction indicated by the arrow (Figure 1). The arrow was presented on either side of the central cross (where the participants were asked to direct their gaze throughout the task) and pointed either to the left or to the right. The two irrelevant dimensions (position and direction indicated by the arrow) gave rise to four experimental conditions depending on whether they were compatible or incompatible with the response to the colour (see Figure 1, from left to right): compatible direction-compatible position (CDCP), incompatible direction-compatible position (IDCP), compatible direction-incompatible position (CDIP) and incompatible direction-incompatible position (IDIP). The same numbers of trials were run for all four conditions (80 per condition). Two irrelevant dimensions were used to increase the difficulty of the task [46], in order to maximize the possibility of finding differences between healthy participants and aMCI patients.

After a practice block of 24 trials, a total of 320 trials (80 per condition) were presented in two blocks, with an inter-block interval of 90 s. The response button assigned to each colour of the stimulus was counterbalanced among the participants, and they were instructed to respond as quickly and accurately as possible. Half of the participants were asked to press the left button with the left hand when a red arrow appeared and the right button with the right hand when a blue arrow appeared, whereas the other half were instructed to respond in the opposite way.

Figure 1 about here

EEG recordings

In the EEG recordings, a total of 47 active electrodes were used, in accordance with the 10-10 International System: at AFz, AF7, AF8, Fz, F3, F4, F5, F6, F7, F8, FCz, FC1, FC2, FC3, FC4, FT7, FT8, FT9, FT10, Cz, C1, C2, C3, C4, C5, C6, T7, T8, CPz, CP3, CP4, TP7, TP8, TP9, TP10, Pz, P3, P4, P7, P8, P9, P10, PO7, PO8, Oz, O1 and O2. The EEG signal was passed through a 0.01–100 Hz analog bandpass filter, and was sampled at 500 Hz. The reference electrode was placed on the tip of the nose and the ground electrode was placed at Fpz. Simultaneously to EEG recordings, ocular movement (EOG) recordings were obtained with two electrodes located supra- and infraorbitally to the right eye (VEOG) and another two electrodes at the external canthus of each eye (HEOG). All impedances were maintained below 10 kΩs. After signal storage, the blinks were corrected off-line by use of the algorithm of Gratton et al. (1983) [47]. The signal was passed through a 0.01–30 Hz digital band-pass filter. Epochs with signals exceeding ±100 μV were automatically rejected, and all remaining epochs were inspected individually to identify those still displaying artifacts; the epochs showing artifacts were also excluded from subsequent averaging. Epochs were then corrected to the mean voltage of the baseline (-200 to 0 in stimulus-locked ERPs, -800 to -600 in response-locked ERPs).

Data analyses

Trials with incorrect responses or RTs outside the 100-1200 ms range were excluded from the analysis. The RT, the magnitude of interference (defined as the difference in the RT between one condition with incompatibility of direction and/or position and the RT in the condition of double stimulus-response compatibility, i.e. the CDCP condition) and the percentage of incorrect responses were analysed.

Epochs were established between -200 and 800 ms, for waveforms associated with presentation of the stimulus (N2pc), and between -800 and 300 ms, for waveforms associated with the response (LRP-r). Following previous studies [48], a two-step procedure was used to remove epochs with horizontal ocular artifacts in stimulus-locked waveforms. Firstly, trials with large horizontal eye movements (larger than ± 30 μV) were removed. Secondly, averaged HEOG waveforms showing residual eye movements (HEOG activity exceeding ± 3 μV) were eliminated. Epochs with amplitude values outside ± 100 μV were excluded from the analysis, and the remaining epochs were visually examined to reject those presenting artifacts. The mean number of averaged epochs on each experimental condition was 65 for the CG and 63 for the aMCI group in stimulus-locked ERPs and 69 for the CG and 66 for the aMCI group in response-locked ERPs.

To obtain the LRP-r, the difference in contralateral-ipsilateral activation for the primary motor cortex in each hemisphere was calculated. The differences were then averaged [49]. The method can be summarised by the formula: $[(C4 - C3)_{\text{left hand movements}} + (C3 - C4)_{\text{right hand movements}}] / 2$. Deflections with negative polarity indicate correct preparation of the response. N2pc was obtained according to the hemifield of stimulus presentation [17], that is, $[(PO8 - PO7)_{\text{left hemifield}} + (PO7 - PO8)_{\text{right hemifield}})] / 2$.

The N2pc peak latency was identified as the largest negative peak between 200-375 ms after stimulus presentation. The N2pc amplitude was calculated as the averaged amplitude between 250-350 ms (based on the inspection of the grand averages and the statistics values of peak latency).

The onset latency of correct preparation of the LRP-r was analysed. The onset was determined by the method of Schwarzenau et al. (1998) [50], which assumes that the onset of correct preparation corresponds to the intersection point of two straight

lines, one fitted to the baseline and another to the rising slope of the LRP. The LRP-r amplitude was obtained as the mean amplitude between -125 and -25 ms regarding the response.

The stimulus-locked lateralized readiness potential (LRP-s) was not analysed because the overlap between LRP and central contralateral negativity (N2cc) does not allow reliable measurement of the onset of LRP-s [51,52]. Nevertheless, LRP-r onset was measured because N2cc is observed at stimulus-locked averages and therefore it is jittered at response-locked averages [53].

Statistical analyses

With the aim of examining whether there were any differences in the RTs or the percentage of errors (PE) according to the Experimental conditions and Diagnosis, mixed measures ANOVAs were applied with two within-subject factors: Position (two levels: Compatible and Incompatible) and Direction (two levels: Compatible and Incompatible), and one inter-subject factor: Diagnosis (CG and aMCI group). A mixed measures ANOVA was conducted for the magnitude of the interference in the three conditions where a SRC was present (IDCP, CDIP, IDIP), with one within-subject factor: Condition (three levels: IDCP, CDIP, IDIP), and one inter-subject factor: Diagnosis (two levels: CG, aMCI).

Mixed measures ANOVAs were applied to N2pc latency and amplitude, with two within-subject factors: Position (two levels: Compatible and Incompatible) and Direction (two levels: Compatible and Incompatible), and one inter-subject factor: Diagnosis (two levels: CG and aMCI group).

With the aim of examining possible differences in the onset latency of the preparation of the correct response in the LRP-r, as well as LRP-r mean amplitudes, corresponding mixed measures ANOVAs were carried out for each, with two within-

subject factors: Position (two levels: Compatible and Incompatible) and Direction (two levels: Compatible and Incompatible), and one inter-subject factor: Diagnosis (two levels: CG and aMCI group).

Receiver Operating Characteristics curves (ROC, including sensitivity and specificity indexes) were calculated for those ERP parameters that showed Diagnosis to have a significant effect (i.e. N2pc and LRP amplitudes).

A Greenhouse-Geisser ε correction for the degrees of freedom was performed where necessary, and the corresponding α levels were determined. When the ANOVAs revealed significant effects due to the factors and their interactions, posterior comparisons of the mean values were carried out by paired multiple comparisons (adjusted to Bonferroni).

Results

Behavioural measures

For the RT (see Table 1), the mixed measures ANOVA (Position x Direction x Diagnosis) revealed a significant effect of Position ($F(1, 50) = 162.3$, $p < 0.001$, $\eta^2_\rho = 0.764$), as the RT was slower when the Position was Incompatible than when it was Compatible with the required response ($p < 0.001$). The Diagnosis factor did not reveal a significant effect in RT ($F(1, 50) = 2.55$, $p = 0.11$, $\eta^2_\rho = 0.049$).

For the percentage of errors (PE) (see Table 1), the mixed measures ANOVA (Position x Direction x Diagnosis) revealed that Position had a significant effect ($F(1, 50) = 59.9$, $p < 0.001$, $\eta^2_\rho = 0.545$), as the PE was higher in trials with Incompatible Position than in trials with Compatible Position ($p < 0.001$).

For the magnitude of the interference, the mixed measures ANOVA (Interference x Diagnosis) revealed that the type of Interference had a significant effect ($F(2, 100) = 73.2$, $p < 0.001$, $\eta^2_\rho = 0.594$), as the interference was greater in CDIP than

in IDCP ($p < 0.001$), and it was greater in IDIP than in IDCP ($p < 0.001$). Diagnosis did not exert significant effects.

Table 1 about here

ERPs

For the N2pc latency, the mixed measures ANOVA (Position x Direction x Diagnosis) did not reveal any significant effects. For the N2pc amplitude, the mixed measures ANOVA (Position x Direction x Diagnosis) revealed that Diagnosis had a significant effect ($F (1, 50) = 6.15$, $p = 0.017$, $\eta^2_\rho = 0.11$), as the N2pc amplitude was smaller in the aMCI than in the CG participants ($p = 0.017$) (see Table 1 and Figure 2).

Figure 2 about here

Regarding the LRP-r onset latency, the mixed measures ANOVA (Position x Direction x Diagnosis) showed that Position had a significant effect ($F (1, 50) = 49.7$, $p < 0.001$, $\eta^2_\rho = 0.498$), as the LRP-r onset was earlier when the Position was Compatible than when it was Incompatible with the required response ($p < 0.001$). The mixed measures ANOVA (Position x Direction x Diagnosis) for the LRP-r mean amplitude revealed that Diagnosis had a significant effect ($F (1, 50) = 18.9$, $p < 0.001$, $\eta^2_\rho = 0.275$), as the LRP-r amplitude was larger in CG than in the aMCI group ($p < 0.001$) (see Table 1 and Figure 3). The Position had also a significant effect ($F (1, 50) = 10.1$, $p = 0.001$, $= \eta^2_\rho$ 0.195), as the amplitude was larger when the position was Compatible than when it was Incompatible with the response ($p = 0.001$).

Figure 3 about here

ROC analysis for N2pc amplitude (see Figure 4, left panel) revealed an area under curve (AUC) of 0.66. Using the value of -1.88 μV as a cut-off, the indexes of sensitivity and specificity were 0.78 and 0.52 respectively. ROC analysis for LRP-r

amplitude (see Figure 4, right panel) yielded an AUC of 0.86. Using the value of -3.75 μV as a cut-off, the sensitivity and specificity indexes were 0.85 and 0.92 respectively.

Figure 4 about here

Discussion

The aim of the present study was to search for ERP markers of aMCI by studying healthy elderly and aMCI patients while they performed a Simon task. The main results were as follows: a) the behavioural measures (Reaction Time, Percentage of Errors and Interference) did not evidence differences between the CG and aMCI participants; b) the N2pc amplitude was smaller in aMCI than in CG; c) The LRP-r amplitude was smaller in aMCI than in CG, constituting a marker of aMCI with an area under curve (AUC) of 0.86.

The Reaction time (RT) and the Percentage of Errors (PE) were not different between healthy and aMCI patients. Likewise, differences between both groups were not found in the magnitude of the interference. These results are consistent with previously reported preserved inhibitory control in aMCI patients [54-56, but see also 31,32]. Although two irrelevant dimensions were used in the present study, in order to maximize differences in performance, the present behavioural data did not distinguish between normal ageing and aMCI.

The position of the arrow caused a Simon effect (longer RT and higher PE when it was incompatible with the response side). This is consistent with previous findings using samples of young [51,57] and elderly [34] participants. However, interference from the direction (in IDCP condition) was not significant. This result was inconsistent with previous results in a sample of young adults performing an identical task [58]. Nonetheless, in that study interference from the position was greater than interference from the direction, as the stimulus position attracts attentional resources more

automatically and rapidly than the direction [45,59], which partially would mask the effect of the direction. In the present study, it is possible that a greater age-related decline for effortful than for automatic processes [60] increased the above masking and nullified the direction effect, as would be consistent with results obtained in samples of healthy middle-aged and elderly participants performing an identical task [61]. On the other hand, effect of the position-direction interaction (in the IDIP condition) was not significant, as also found in previous studies [58,62].

Electrophysiological measures showed that motor response execution stage was not longer in aMCI patients than in healthy participants (i.e. differences in LRP-r onset were not present), which is consistent with the absence of any differences in reaction times between both groups. On the other hand, the incompatibility of the position delayed the LRP-r onset, demonstrating interference from this irrelevant dimension at the response execution stage, as previously suggested on the basis of behavioural data [63,64].

The amplitude of the LRP-r was smaller in aMCI patients than in healthy participants. As far as we know, this is the first study focusing on LRP amplitudes in aMCI patients, and consequently the first report of smaller LRP amplitudes in aMCI than in healthy participants. Importantly, the LRP-r amplitude may be of clinical interest from a diagnostic point of view, since it yielded good indexes of sensitivity and specificity, 0.85 and 0.92 respectively for a cut-off of -3.75 μV. It is important to notice that the LRP is obtained by a non-invasive procedure through a relatively inexpensive and widely used technique, i.e. the ERP.

In previous studies, larger LRP amplitudes in healthy elderly participants than in young participants had been associated with reduced inhibitory control [26]. However, larger LRP amplitudes were found when the stimulus position was compatible with the

response, and shorter RT and lower PE were observed. In other words, larger LRP amplitudes were associated with behavioural indexes of better inhibitory control. Also, consistent with this observation, the smaller LRP amplitudes in aMCI patients may be related to incipient impairment of the implementation of motor resources for executing the response, which would still not be manifested in the behavioural performance. This interpretation is consistent with recent reports of deficits in motor regions in MCI patients, observed in transcranial magnetic stimulation (TMS) studies [29,65,66]. Thus, the results of the present study are consistent with the view of MCI patients showing deficits in the motor cortex, as revealed by LRP-r amplitude, which may also constitute an early electrophysiological marker of the aMCI state.

The timing of visuospatial processing of the target stimulus, whose ERP correlate was N2pc latency, did not reveal any differences between participants according to the diagnosis. No previous studies have focused on N2pc latency in aMCI patients. Therefore, on the basis of the evidence of the present results, it may be concluded that the speed of attentional shifts to target stimuli is not affected in amnestic MCI patients.

The N2pc amplitude was smaller in aMCI patients than in healthy participants, a result that suggests a reduced allocation of attentional resources to the target stimulus in the aMCI patients. Therefore, aMCI patients might have impairment in the brain areas that generate the N2pc component, basically temporal and parieto-occipital regions (for details on the N2pc sources see Hopf et al. (2000) [67] and Lorenzo-López et al. (2011) [21]). This result is consistent with behavioural evidence for declined visuospatial abilities in aMCI patients [11]. Furthermore, some authors have suggested that visuospatial deficits may take place earlier than the typical memory impairments in early stages of the AD [68,69]. Although data from ROC analyses did not show

sufficient AUC to consider N2pc amplitude as a good aMCI biomarker, the N2pc amplitudes suggest that the aMCI patients exhibit anomalies in brain activity related to visuospatial processing of a target stimulus and constitute therefore a brain correlate of aMCI.

Some studies have shown that N2pc may reflect activity related to processing of the target as well as suppression of the non-target [15]. Thus, the previously mentioned deficits in aMCI participants may be related to target processing and also to suppression of the non-target stimulus. However, when a single contralateral non target appears in the display (as in the Simon task of the present study), the N2pc waveform basically reflects activity related to target processing [14]. This is further suggested by considering the distance between target and non target in the task used in the present study (7.5º). Since receptive fields in the extrastriate cortex are comprised between 3º-8º of visual angle [70], competition between target and non-target is unlikely to occur. Thus, the decreased N2pc amplitude observed in aMCI patients was probably due only to impairment in the allocation of attentional resources to the target stimulus.

Finally, in a previous study where young adults performed an identical task [58], N2pc was modulated by a conflict of spatial information conveyed by both irrelevant dimensions (i.e., N2pc was smaller when the direction of the arrow pointed to the opposite side regarding the hemifield where it was located). In the present study the absence of N2pc amplitude modulations can be easily explained since direction effects were not present. Moreover, consistently with other reports, N2pc was not modulated by interference from the stimulus position [22,51].

Conclusions

In summary, the present study investigated visuospatial and motor correlates of aMCI during the performance of a Simon task by 25 healthy participants and 27 aMCI

patients. Although behavioural differences were not evidenced between healthy and aMCI groups, electrophysiological correlates of cognitive processes showed an incipient decline in aMCI patients, suggesting that brain changes may start earlier than the affectation of the behavioural performance. Regarding visuospatial processes, the speed of attentional shifts to the target stimulus (N2pc latency) was similar in aMCI patients and healthy participants. However, the N2pc amplitude, an index of the amount of attentional resources devoted to the target stimulus, was smaller in the aMCI than in the control group, which suggests impairment of the neural sources of the N2pc component (i.e. in temporal and parieto-occipital regions) in aMCI patients. Moreover, consistently with absence of significant differences in RTs, the time of response execution was not elongated in aMCI participants. However, the LRP-r amplitude was smaller in aMCI patients than in healthy participants, suggesting impairment of frontal motor areas. Furthermore, the ROC curves suggest that LPR-r amplitude may constitute a good biomarker of aMCI (indexes of sensitivity and specificity were 0.85 and 0.92, respectively).

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Figure legends

Figure 1: **The Simon task with stimuli presented and response buttons**. Participants were instructed to respond by pressing the left button with the left hand when a red arrow appeared, and the right button with the right hand when a blue arrow appeared, so that the conditions presented (from left to right) were, respectively, as follows: compatible direction and compatible position (CDCP); incompatible direction and compatible position (IDCP); compatible direction and incompatible position (CDIP), and incompatible direction and incompatible position (IDIP). The response buttons were counterbalanced between participants.

Figure 2: **The negativity posterior contralateral (N2pc).** The N2pc at the PO7/PO8 electrode pair is represented for the CG (solid line) and the aMCI (dashed line) in the four conditions of the task (CDCP, IDCP, CDIP and IDIP). The N2pc amplitude was smaller in aMCI patients than in CG, which revealed reduced visuospatial processing in aMCI participants. No differences in N2pc latency were observed.

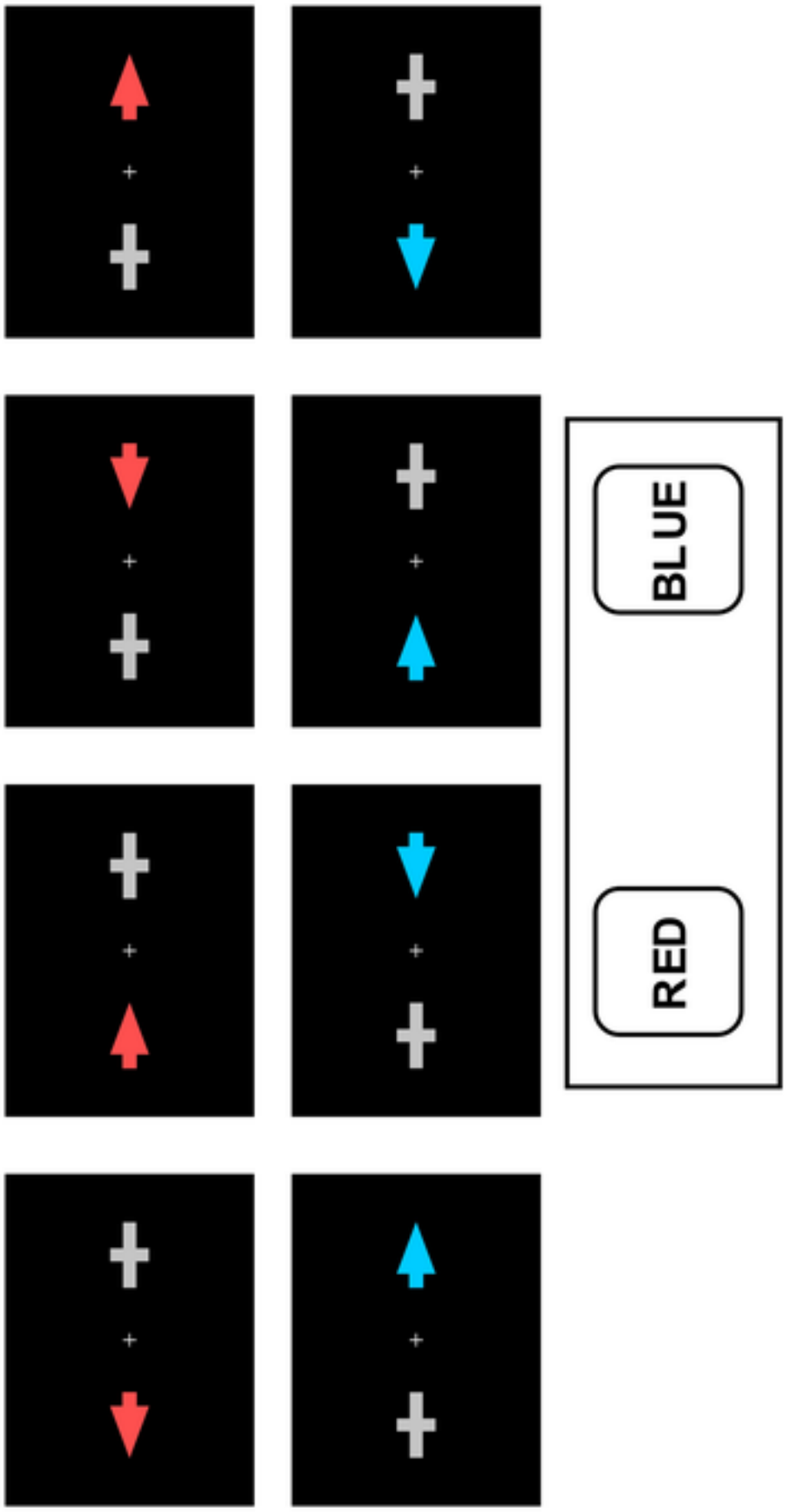
Figure 3: **The response-locked lateralized readiness potential (LRP-r).** The LRP-r is represented for the CG (solid line), and aMCI (dashed line) in the four conditions of the task (CDCP, IDCP, CDIP and IDIP). The LRP-r onset latency (the point where starts the negative trend in the waveform) and LRP-r mean amplitude (-125 - -25ms) were calculated. The LRP-r amplitude was larger in healthy participants than in aMCI patients, suggesting declined mechanisms for implementing the response in aMCI patients.

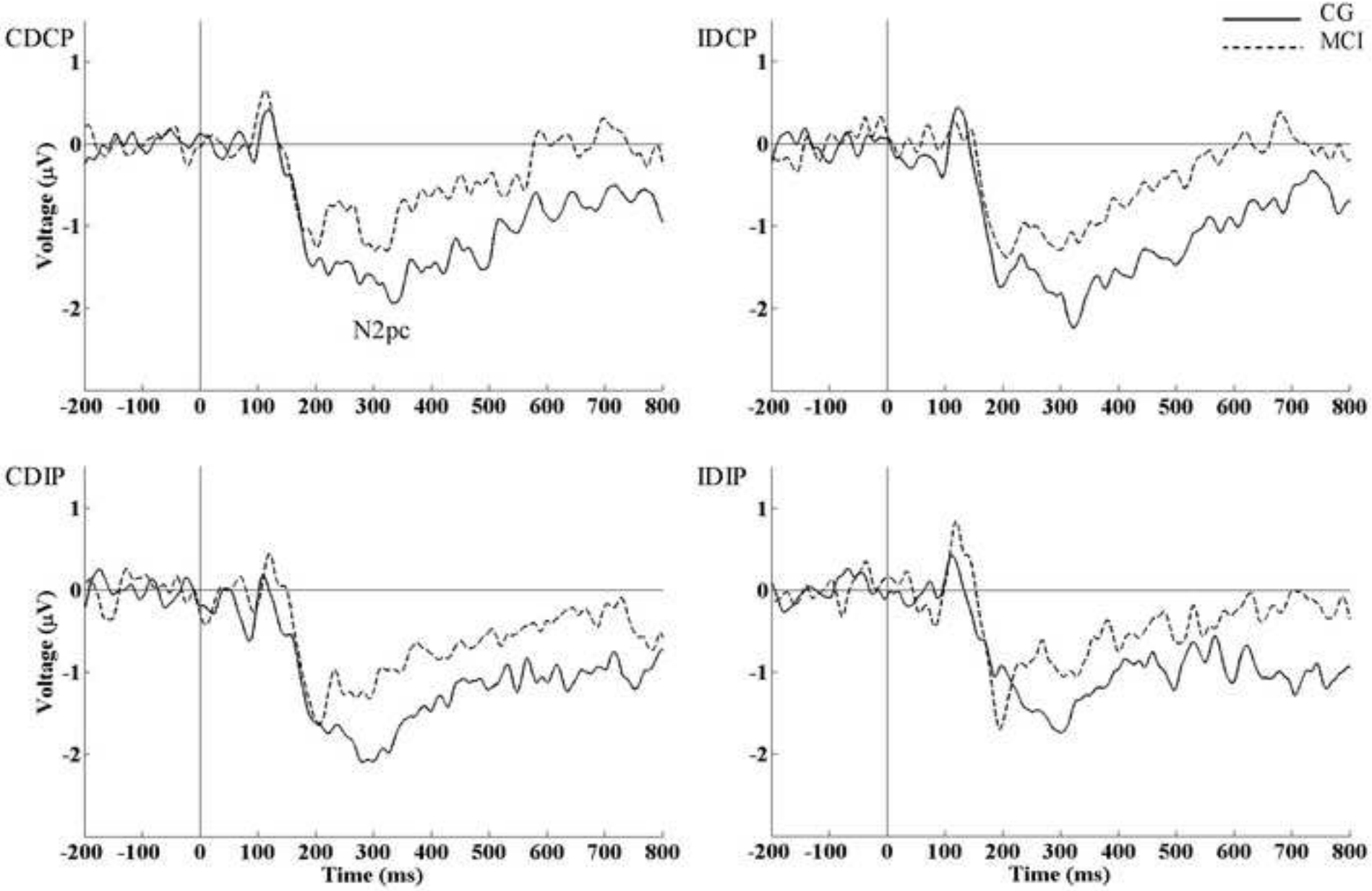
Figure 4: **aMCI correlates and biomarkers**. Receiver operating characteristics curves (ROC) are represented for LRP amplitude (top) and N2pc amplitude (bottom). Indexes of sensitivity and specificity, and area under curve (AUC) are reported for LRP and N2pc amplitudes respectively. For the LRP amplitude, the selected cut-off was -3.75 μV (sensitivity: 0.85, specificity: 0.92). For the N2pc amplitude, the selected cut-off was -1.88 μV (sensitivity: 0.78, specificity: 0.52).

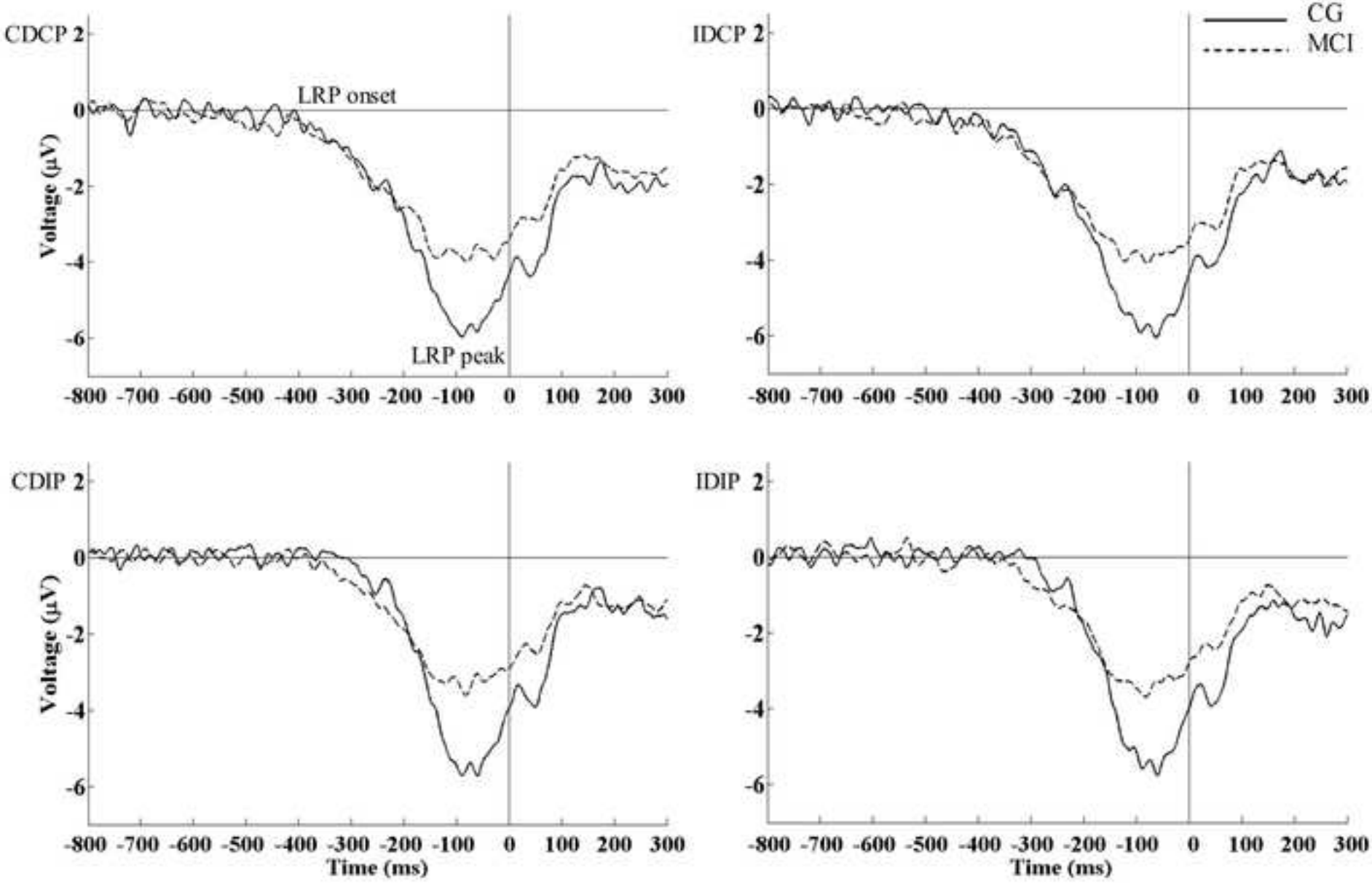
Table

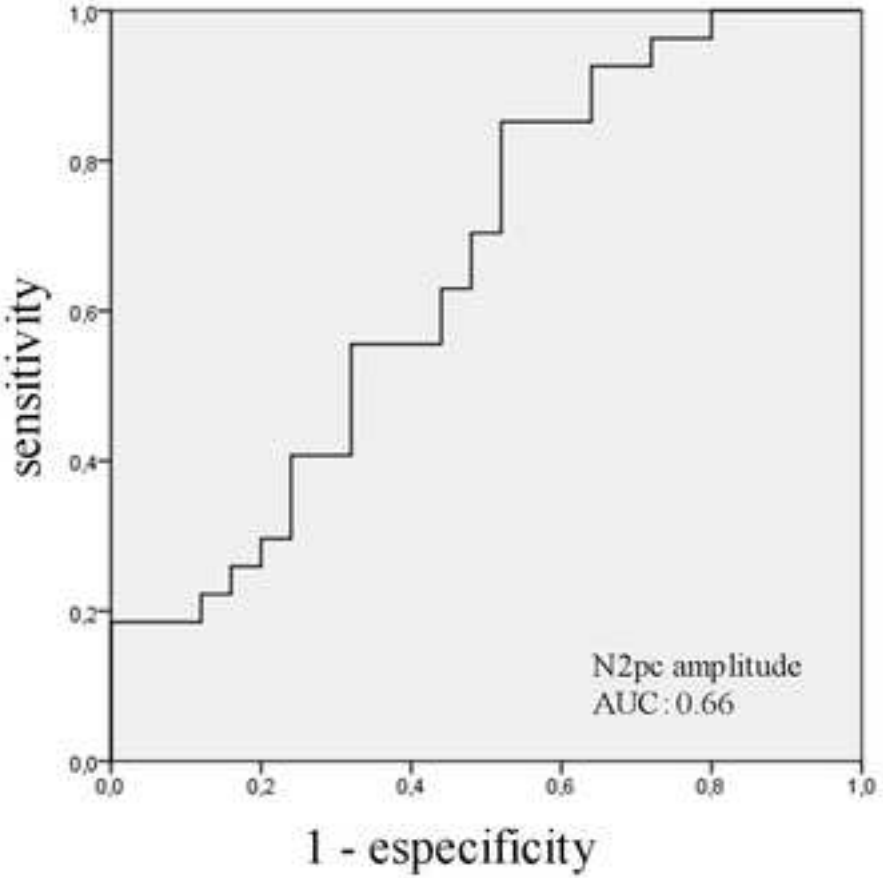
	RT	PE	N2pc lat	N2pc amp	LRP onset	LRP amp
CG CDCP	546 (86)	2.9 (3.9)	301 (42)	-2.5 (1.6)	-316 (71)	-5.6 (1.9)
CG IDCP	551 (80)	3.0 (3.9)	301 (31)	-2.4 (1.9)	-289 (59)	-5.7 (1.7)
CG CDIP	600 (88)	8.3 (6.2)	290 (40)	-2.5 (1.8)	-241 (46)	-5.3 (1.9)
CG IDIP	595 (86)	6.4 (6.6)	292 (44)	-2.2 (1.7)	-245 (41)	-5.3 (2.0)
MCI CDCP	589 (107)	3.3 (4.4)	310 (43)	-1.5 (1.1)	-336 (82)	-3.8 (1.6)
MCI IDCP	596 (115)	3.6 (4.2)	310 (32)	-1.5 (1.4)	-319 (74)	-3.9 (1.5)
MCI CDIP	645 (126)	8.1 (6.3)	297 (38)	-1.7 (1.2)	-288 (76)	-3.2 (1.3)
MCI IDIP	643 (127)	8.0 (5.5)	316 (36)	-1.2 (1.1)	-278 (72)	-3.4 (1.6)

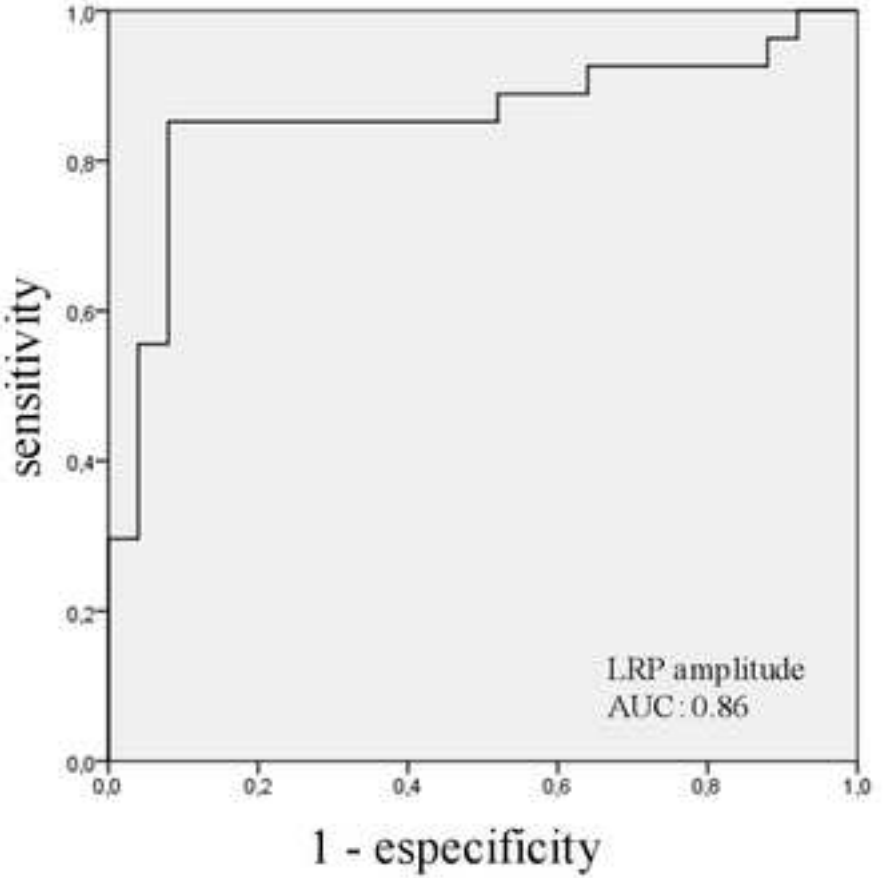
Table 1- Mean and standard deviation, for each Condition (Compatible Direction-Compatible Position (CDCP), Incompatible Direction-Compatible Position (IDCP), Compatible Direction-Incompatible Position (CDIP) and Incompatible Direction-Incompatible Position (IDIP)) and group (Control Group (CG) and Mild Cognitive Impairment (MCI)) of Reaction Time (in milliseconds); Percentage of Errors (PE); peak latency and averaged amplitude (measured as averaged amplitude between 250-350 ms) of N2pc at PO7/PO8 electrodes pair; onset of the response-locked lateralized readiness potential (LRP-r) and LRP-r amplitude (averaged amplitude between -125 – -25 ms) at C3/C4 electrodes pair.


BLUE
RED


CDCP
IDCP
CG
MCI
N2pc
CDIP
IDIP
Voltage (μV)
Time (ms)
1
0
-1
-2
-200
-100
0
100
200
300
400
500
600
700
800


CDCP 2
IDCP 2
CDIP 2
IDIP 2
CG
MCI
LRP onset
LRP peak
Voltage (μV)
0
-2
-4
-6
-800 -700 -600 -500 -400 -300 -200 -100 0 100 200 300
Time (ms)


sensitivity
1 - especificity
N2pc amplitude
AUC: 0.66
0,0
0,2
0,4
0,6
0,8
1,0


sensitivity
1 - especificity
LRP amplitude
AUC: 0.86
0,0
0,2
0,4
0,6
0,8
1,0

3. General Discussion

The first part of this section is devoted to the results obtained in the basic psychophysiological studies with samples of young participants, who performed the SRC-p, SRC-d, and SRC-pd tasks. Secondly, the discussion is focused on the changes related with healthy ageing and the MCI (in samples of participants who performed the SRC-pd task).

3.1 Basic psychophysiological studies

3.1.1 Insights on N2cc and N2pc modulations in Simon tasks

For the SRC-p and the SRC-pd tasks, the behavioural results showed a Simon effect, i.e. longer Reaction Time, RT, when the stimulus position (irrelevant characteristic of stimulus) was incompatible than when it was compatible with the response to the colour (relevant characteristic of stimulus). These results were consistent with findings widely replicated by previous behavioural studies (for reviews, see Lu & Proctor, 1995; Simon, 1990).

In the Study 1 on the SRC-p task (Cespón et al., 2012), the waveforms free of motor activity (the procedure to remove the motor activity was explained in Study 1, Figure 2) allowed studying (in absence of overlap with the LRP component) how N2cc and N2pc components were modulated according to the compatibility/incompatibility between the stimulus position and the required response. These waveforms showed that the N2cc amplitude was larger in IP-NP (incompatible position minus neutral position condition) than in CP-NP (see Study 1, Figure 4). This result was consistent with a greater activity related with the cognitive control for monitoring the selection of the correct response in the IP compared to the CP condition.

N2cc had been related with preventing a response biased by the change of spatial attention to the target stimulus. Thus, in this condition a greater activity in the incompatible condition was expected because the hand to execute the required response was spatially contralateral regarding the attentional shift and consequently, a greater activity was needed for preventing a cross-talk between the direction of the spatial attention and the manual response preparation. Therefore, and in line with the suggestion of Leuthold and Schröter (2006), it was proposed that N2cc represents a mechanism involved in cognitive control that acts monitoring the selection of the correct response.

In addition, the eLORETA analyses revealed greater activity between 150 and 200 ms in premotor regions in CP and IP (i.e., the lateralized conditions) than in the NP condition (where the stimulus was in the centre of the screen) (see Study 1, Figure 5). This activity appears to be related to the N2cc component since it was observed in the spatially lateralized conditions (CP and IP) in which N2cc activity was expected to emerge for preventing the automatic selection and execution of the response based on the direction of the spatial attention to the target stimulus position. In the NP condition the response was not accompanied by a change of spatial attention (as the stimulus was placed on the centre of the screen). Thus, activity for suppressing the spatial tendency of response was not necessary in that condition.

Even if the eLORETA results should be considered with caution in light of its low spatial resolution, the activity was estimated in a region consistent with the sources of N2cc, the dorsal premotor cortex (dPM) (see Praamstra & Oostenveld, 2003), and within the temporal window in which N2cc was expected to appear (Leuthold & Schröter, 2006). Moreover, the premotor activity observed in eLORETA analyses was lateralized to the left hemispheric. This fact was consistent with previous studies that

had suggested that the left hemisphere makes a greater contribution to the N2cc than the right hemisphere (Praamstra & Oostenveld, 2003) as well as with the lateralization of the dPM activity to the left hemisphere during monitoring the response selection (Johansen-Berg et al., 2002; Rushworth, Nixon, Wade, Renowden, & Passingham, 1998; Schluter, Rushworth, Passingham, & Mills, 1998).

On the other hand, N2pc was not modulated by the experimental manipulation. This indicated that the Simon effect does not occur in the visuospatial processing of the relevant stimulus (Praamstra & Oostenveld, 2003; Van der Lubbe & Verleger, 2002). eLORETA showed evidence for differences in N2pc activity between lateralized and neutral stimuli (such evidence was only partial since a greater parietal activity was found in the compatible than in the neutral condition but differences between the incompatible and the neutral conditions were not found, see Study 1, Figure 5). Importantly, a functional dissociation between N2pc and N2cc components was obtained by the fact that N2cc, but not N2pc, was differentially affected by the experimental condition. The lack of modulation of N2pc component by the stimulus position was consistent with results from the study with the SRC-pd task, which showed that the stimulus position did modulate neither N2pc peak latency nor N2pc amplitude.

In fact, using the SRC-pd task, it was observed that N2pc amplitude was smaller in the S-S incompatible conditions (i.e., IDCP and CDIP) than in the S-S compatible conditions (i.e., CDCP and IDIP) (see Study 2, Figure 1f and Figure 2). These findings revealed interference in the visuospatial processing of the target stimulus, caused by S-S incompatibility. Concretely, in the S-S incompatible conditions (IDCP and CDIP), the direction indicated by the arrow and the position of the arrow conveyed contradictory spatial information (the arrow was pointing to the opposite hemifield with respect to the arrow location). Thus, the irrelevant dimensions induced opposing changes in spatial

attention (Klein & Ivanoff, 2011), so that the ability to allocate attentional resources to the target stimulus was reduced in these conditions. These findings were consistent with N2pc modulation by high-level properties of the display (Eimer & Kiss, 2007; Telling, Kumar, Meyer, & Humphreys, 2009).

Also, the modulation of N2pc by S-R incompatibilities could be easily excluded because, if N2pc would have been modulated by the stimulus position then the amplitude of N2pc would have been smaller in S-R incompatible position (IDIP and CDIP, in which the stimulus position was incompatible with the response) than in S-R compatible position (CDCP and IDCP, in which the stimulus position was compatible with the response). Also, if N2pc would have been modulated by arrow direction, then the N2pc amplitude would have been smaller in S-R incompatible direction (IDCP and IDIP, in which the direction indicated by the arrow was incompatible with the response) than in S-R compatible direction (CDCP and CDIP, in which the direction pointed by the arrow was compatible with the response). The lack of N2pc amplitude modulation by the Simon effect (i.e., SRC based on stimulus position, or SRC-p) is consistent with the previous findings (Cespón et al., 2012; Praamstra, 2006; Praamstra & Oostenveld, 2003; Praamstra & Plat, 2001; Van der Lubbe & Verleger, 2002). Also, based on these results, it may be suggested that the N2pc was probably modulated by an S-S conflict and not by the Simon effect in Valle-Inclán (1996, exp 2).

In accordance with the recent literature on N2pc (Hillimire, Mounts, Parks, & Corballis 2009, 2010; Telling et al., 2009), we interpreted the smaller N2pc amplitude as reflecting diminished target processing due to the S-S interference. As in the present study target and non-target stimuli were separated by a visual angle of 7.5º, it is possible that N2pc basically reflected processes associated with identification of the target more than processes related with non-target suppression (see Hickey et al., 2009). On the

contrary, in Valle-Inclán (1996, exp 2) target and non-target were separated by 1º of visual angle. Thus, processes related to suppression of the non-target might have influenced the N2pc amplitude modulation in that study, which would explain the increase of amplitude when S-S conflict was present.

Finally, influence of declined visuospatial processing on the RTs was scarce and not significant. It might have been masked by both S-R effects (i.e., by incompatibilities from the stimulus position and from the direction pointed by the arrow), which seems modulating motor processes; concretely, the response selection and the response execution stages.

3.1.2 Interference loci from stimulus position and arrow direction

A third study (Study 3, Cespón et al., under review, a) was conducted for examining the similarities, and possible differences, between both types of S-R interferences (i.e., interference from the stimulus position and interference from the direction pointed by the arrow), which had been considered equivalent by ERP studies in spite of the evidence on the existence of behavioural differences between them. Therefore, as pointed in the section of Introduction, the SRC-p and SRC-d tasks (which were designed under an identical experimental design) were compared.

The results showed that both tasks elicited interference in the incompatible conditions (slower RT and higher PE in the incompatible than in the compatible conditions). That interference was greater in the SRC-p than in the SRC-d task, which was consistent with the results observed in the SRC-pd task (Cespón et al., 2013). That is, a greater interference due to stimulus position than to the arrow direction was found. These differences were consistent with the behavioural results observed in previous studies using similar tasks (Galashan et al., 2008; Wittfoth et al., 2009). Also, a

facilitation effect was obtained in the compatible condition of the SRC-d task (consistently to previous studies, e.g. Masaki et al., 2000) but not in the SRC-p task (see Study 3, Figure 2).

The interference effect related with the stimulus position was similar throughout the distribution of RTs (i.e., from faster to slower RTs) whereas that the interference from the arrow direction increased to slowed responses (see Study 3, Figure 2). These results were consistent with those observed in previous studies for both types of task (for a revision on the distributional analysis in Simon-type tasks, see Proctor et al., 2011). According to previous studies (Iani et al., 2011; Symes et al., 2005; Vainio et al., 2007), the arrow would take more time in affecting the performance since it requires the interpretation of a symbolic meaning. Therefore, the stimulus position, in comparison to the direction pointed by the arrow, seems to attract attentional resources in a more automatic and fast way, as reported by previous studies (Abrahamse & Van der Lubbe, 2008; Klein & Ivanoff, 2011). For this reason, the stimulus position affected the performance from faster RTs.

In accordance with behavioural data the ERP results revealed similarities but also differences between the two SRC tasks. Specifically, the stimulus position and the direction of the arrow shared a common locus of interference in the response execution stage, as observed in the LRP-r waveforms. Specifically, in both tasks, the LRP-r onset was delayed in the incompatible condition with respect to the neutral and compatible conditions. Likewise, in both tasks, that delay was preceded by a transient preparation of the incorrect response (see Study 3, Figure 5) that did not achieve the threshold for responding. These results were consistent with those obtained in previous studies using SRC-d-type tasks (Masaki et al., 2000). Also, interference in the response execution stage for incompatibility from the stimulus position had been suggested on the basis of

behavioural data (Ansorge & Whur, 2004; Vallesi, Mapelli, Schiff, Amodio, & Umiltà, 2005). In sum, interference in the response execution stage was a shared locus of interference for both types of S-R incompatibilities.

On the other hand, interference from the stimulus position (i.e., in the SRC-p task) was related to longer P3b latencies and smaller P3b amplitudes in the incompatible condition in comparison to the compatible and neutral conditions. However, the P3b component was not modulated in the SRC-d task. Analyses of P3b distinguishing for responses with fast RT and slow RT (where the magnitude of the interference was similar for both types of S-R incompatibility) showed consistent results. That is, the stimulus position, but not the direction pointed by the arrow, modulated the P3b latency and amplitude. Consequently, it can be stated that these differences were not due to the magnitude of the interference effect. P3b modulation by stimulus position was consistent with previous results in which P3b latency (Leuthold & Schröter, 2006; Leuthold & Sömmer, 1999; Melara et al., 2008; Ragot, 1990; Valle-Inclán, 1996; Van der Lubbe & Verleger, 2002) and P3b amplitude (Leuthold & Schröter, 2006; Ragot, 1990; Valle-Inclán, 1996) had been modulated by the stimulus position. Contrarily, the absence of P3b modulation by arrow direction was inconsistent with previous studies that showed longer P3b latency (Masaki et al., 2000) and smaller P3b amplitude (Galashan et al., 2008) for the incompatibility from the direction.

Previous studies that found P3b modulations associated with the incompatibility from the direction of the arrow used a lesser proportion of incompatible than compatible and/or neutral trials. Therefore, it cannot be excluded that P3b modulations were a result of the used oddball-type design (see Melara et al., 2008) or even due to increased interference related with sequence effects (Davelaar & Stevens, 2009; Spapé, Band, & Hommel, 2011). Importantly, the lack of modulation on P3b latency in the SRC-d task

was consistent with findings from studies that used semantic stimulus-response incompatibility tasks (Magliero, Bashore, Coles, & Donchin, 1984; Ragot & Fiori, 1994) and indicated a non-common interference locus for the stimulus position and the arrow direction. In addition, the modulation of the P3b latency by the stimulus position was consistent with the high sensitivity of P3b latency for the Simon effect (Verleger, 1997).

Altogether, the results of the Study 3 pointed to electrophysiological similarities and differences between interference from the stimulus position and interference from the direction pointed by a central arrow. Specifically, the two irrelevant dimensions modulated motor processes at the response execution stage. However, the stimulus position, but not the direction pointed by the arrow, modulated the P3b component. Finally, this study exemplified how the control of certain experimental variables (e.g. the balanced number of stimuli per condition) can play an important role for obtaining reliable inferences on the S-R interference effects.

3.2 Age-related and aMCI-related changes in a SRC-pd task

In this second part of the discussion the changes related with the ageing and the amnestic Mild Cognitive Impairment (aMCI) are discussed. For studying the mentioned processes, it was implemented the SRC-pd task in samples of middle-aged and elderly healthy participants and aMCI participants. The age-related changes are firstly discussed. Subsequently, the discussion will be focused on the changes related with the aMCI.

3.2.1 Age-related changes

The findings on age-related changes in SRC-pd task performance resulted in a fourth study (Study 4, Cespón et al., in press). A brief summary of the main results on the age-related changes is as follows: a) age-related slowing in RTs (i.e., the elderly responded slower than the middle-aged participants, and the middle-aged slower than the young participants); b) progressive slowing with age in the response execution stage (LRP-r onset); c) slowing in visuospatial processes (N2pc peak) in middle-aged and elderly relative to young participants but no differences between the two older groups; d) similar position interference in the three age groups and direction interference only in the young group (and also in middle-aged for slow responses); e) perceptual conflict by contradictory spatial information, conveyed by the irrelevant dimensions, only in young participants (i.e., in young participants the N2pc was smaller in IDCP and CDIP than in CDCP and IDIP conditions but in the other groups differences in N2pc amplitude were not observed).

An age-related slowing of the RT was observed (longer RT in the elderly than in the middle-aged and young, and longer RT in the middle-aged than in the young participants). Those results were consistent with the age-related slowing in the performance of Simon-type tasks (Castel et al., 2007; Juncos-Rabadán et al., 2008; Proctor, et al., 2005; Van der Lubbe & Verleger, 2002).

ERP correlates provided evidence about the processes that constituted the loci of the age-related slowing observed in RT. Concretely, the results showed that execution of the motor response represents a locus of age-related slowing as it was suggested in previous ERP studies (Falkenstein et al., 2006; Kolev et al., 2006; Roggeveen et al., 2007; Wild-Wall, Falkenstein, & Hohnsbein, 2008; Yordanova et al., 2004). Specifically, the interval from the LRP-r onset until the time of the overt response was

progressively longer with increased age. Regarding this matter, the present study added that the age-related slowing in the motor execution stage was already manifested in the middle-aged participants (i.e., between 50-64 years old) and that it was further increased in the elderly participants.

Moreover, previous studies had reported that the N2pc component, an electrophysiological correlate of the visuospatial processing of the target stimulus, was delayed in elderly compared to young participants (Amenedo et al., 2012; Lorenzo-López et al., 2008, Lorenzo-López et al., 2011; Van der Lubbe & Verleger, 2002). In fact, in the present study, N2pc peak latency was longer in middle-aged and elderly than in young participants, although no differences between middle-aged and elderly participants were found. Therefore, and consistently with linear regression and correlation analyses conducted for middle-aged and elderly participants, slowing in the response latencies in elderly relative to middle-aged participants may be related with delays in response-related processes (concretely, in the response execution stage) but not with delays in visuospatial processes (see Study 4, Figure 7). Therefore, the results of the present study were consistent with differences in the decline pattern for each cognitive process throughout the life span (Park et al., 2002).

Regarding the interference effect, the RT was shorter and the PE was higher when the stimulus position was incompatible than when it was compatible with the response, consistent with previous findings in samples of young (Lu & Proctor, 1995) and elderly (Proctor et al., 2005) participants. However, age-related increase in interference was not observed, which was not consistent with the findings of previous studies (Bialystok et al., 2004; Castel et al., 2007; Juncos-Rabadán et al., 2008; Proctor et al., 2005; Van der Lubbe & Verleger, 2002) that showed an increase in interference effect with age and supported the inhibitory deficit hypothesis (Hasher & Zacks, 1988;

Zacks & Hasher, 1997). In the present study, the absence of age-related differences in interference might be at least partially related with the direction effect, which was only present in young participants. That is, as middle-aged and elderly participants were not affected by direction interference at the moment of responding to the arrow colour, position-direction interaction (in IDIP) was not possible to occur in the middle-aged and elderly participants. Likewise, the perceptual conflict conveyed by contradictory spatial information (in IDCP and CDIP conditions) would not affect to the two older groups. These factors would reduce the interference in the IDCP, CDIP, and IDIP conditions.

A hypothetical explanation for the absence of direction interference in the two older groups might be offered on the basis of the DA results. Specifically, in the present study, the DA showed that the direction interfered throughout the distribution of RTs in young participants (i.e., from shorter to longer RTs). However, the direction only interfered in slower responses in middle-aged participants and it did not interfere in elderly participants. Therefore, it might be suggested that ageing is related to a disproportionate delay in the speed of processing of the arrow direction (which required a semantic processing, see Iani et al., 2011; Symes et al., 2005; Vainio et al., 2007) compared to the speed of processing of the arrow position (which is more automatically processed, see Klein and Ivanoff, 2011) and colour. Also, this interpretation would be consistent with greater age-related decline in effortful than in automatic processes (Hasher & Zacks, 1979).

ERP correlates of perceptual conflict in allocating attention to the target stimulus (N2pc) and interference in response-related processes (LRP) provided additional information. Firstly, the incompatibility of spatial information conveyed by the two irrelevant dimensions, which occurred in IDCP and CDIP, only modulated the N2pc amplitude in young participants. That is, in the young group the N2pc amplitude was

smaller in IDCP and CDIP than in CDCP and IDIP. However, such differences were not present in the two older groups, which might be related with the above delay in processing the arrow direction. Secondly, the S-R interference from the stimulus position similarly affected the motor execution stage, delaying LRP-r onset in the three age groups, which was consistent with similar levels of behavioural interference. In addition, the incompatibility from the arrow direction also delayed the LRP-r onset in the young participants, which was consistent with behavioural data and with a previous study in a sample of young participants (Masaki et al., 2000) as well as with results obtained in the Study 3 from the SRC-d task. On the other hand, the amplitudes of LRP-r were greater in middle-aged and elderly in comparison to the young participants. Some studies related increased LRP amplitude to declined inhibitory control (Roggeveen et al., 2007) and dysregulation in high-level control systems (Wild-Wall et al., 2008). However, in the present study the increased LRP amplitudes were not accompanied by increased interference. This result might be in line with the compensation hypothesis (Cabeza & Dennis, 2012; Reuter-Lorenz & Cappell, 2008); concretely, the larger LRP amplitudes might be reflecting an additional recruitment of neural sources in the middle-aged and elderly groups in order to maintain good levels of performance.

3.2.2 aMCI-related changes

The main findings discussed in the Study 5 (Cespón, Galdo-Álvarez, and Díaz, under review, b) are the following: a) behavioural measures (reaction time (RT), percentage of errors (PE), and interference) did not evidence differences between the control group (CG) and aMCI participants; b) the N2pc amplitude was smaller in aMCI than in CG; c) The LRP-r amplitude was smaller in aMCI than in CG, constituting a biomarker of aMCI (area under curve (AUC): 0.86).

The behavioural results (RT, PE, interference) could not distinguish between healthy elderly and participants with aMCI. The effects of both irrelevant dimensions were in line with those observed in the study on age-related changes. That is, incompatibility from the stimulus position related with a Simon effect in both groups of participants; however, interference from the arrow direction had no effect. The absence of differences between healthy elderly and aMCI in the interference effect was consistent with previously reported preserved inhibitory control in aMCI participants (Duong, Whitehead, Hanratty, & Chertkow, 2006; Rosano et al., 2004; Zhang, Han, Verhaeghen, & Nilsson, 2007) although other studies did show differences in the performance between healthy and MCI (Davie et al., 2007).

According to the absence of behavioural differences, the analyzed ERP latencies (i.e., N2pc and LRP-r) did not differ according to the diagnostic of the participants. This result indicated that the speed of attentional shifts to lateralized stimuli (N2pc) and the stage of response execution (LRP-r) were not slowed by the aMCI. Contrarily, as specified in the following paragraphs, amplitudes of N2pc and LRP-r did were different between the CG and the MCI participants (see Study 5, Figures 2 and 3).

The amplitude of the LRP-r was smaller in aMCI than in healthy participants. As far as we know, this is the first study focusing on LRP amplitudes in aMCI participants, and consequently the first report of smaller LRP amplitudes in aMCI than in healthy participants. Importantly, the LRP-r amplitude may be of clinical interest from a diagnostic point of view, since it yielded good indexes of sensitivity and specificity, 0.85 and 0.92 respectively for a cut-off of -3.75 μV (see Study 5, Figure 4).

The smaller LRP amplitudes in aMCI participants may be related to incipient impairment of the implementation of motor resources for executing the response, which would still not be manifested in the behavioural performance. Differences in LRP-r

amplitude between the two groups might be related with the reported deficits in motor regions observed using transcranial magnetic stimulation (TMS) (Bracco et al., 2009; Julkunen et al., 2008; Tsutsumi et al., 2012). A complementary interpretation would be that smaller LRP-r amplitudes in aMCI are reflecting loss of compensatory mechanisms, whose existence had been postulated (in the Study 4) for the middle-aged and elderly participants (Cespón et al., in press). Regardless of the specific interpretation, the results of the present study strongly suggest that aMCI participants show deficits in the motor cortex, as revealed by LRP-r amplitudes, which may also constitute an early electrophysiological biomarker of aMCI.

Similarly, the N2pc amplitude was smaller in aMCI than in healthy group. This result suggests a reduced allocation of attentional resources to the target stimulus in aMCI. Therefore, aMCI participants might have impairment in the brain areas that generate the N2pc component, basically temporal and parieto-occipital regions (for details on the N2pc sources see Hopf et al., 2000; Lorenzo-López et al., 2011). This result is consistent with behavioural evidence for declined visuospatial abilities in aMCI participants (Iachini et al., 2009). Although data from ROC analyses did not show sufficient AUC to consider N2pc amplitude as a good aMCI biomarker, the N2pc amplitudes suggest that the aMCI exhibit anomalies in brain activity related to visuospatial processing of a target stimulus and constitute therefore a brain correlate of aMCI.

4. Conclusions

Previous studies did not investigate N2cc modulations in Simon tasks whereas studies on N2pc were scarce and showed contradictory results. On the contrary, the most of studies presented stimuli in a vertical arrangement because it resulted in a more appropriate design for studying the interference locus via LRP. However, N2cc and N2pc deserved to be studied since N2cc seems to be involved in preventing the cross-talk between the direction of the spatial attention and the manual response preparation, which is necessary to correctly responding in the incompatible conditions. In addition, N2pc was related with visuospatial processing of lateralized stimuli and in the Simon task the target stimulus is, in fact, lateralized. Also, effects related with ageing and aMCI were studied. The main findings are summarized in the following points:

1) N2cc is a correlate of cognitive control in the Simon task. This activity is involved in monitoring the selection of the correct response and preventing that the direction of the spatial attention biases the selection of the manual response. Evidence for such conclusion was obtained because, between 150-200 ms, premotor activity, related to N2cc, was greater in the lateralized conditions (CP and IP) than in the neutral condition (NP), as revealed by eLORETA analyses. Also, N2cc was greater in IP than in CP, as evidenced by L-NP waveforms. It was consistent with a greater requirement for monitoring the selection of the correct response when the attentional shift is spatially contralateral regarding the required response.
2) Further evidence for the N2pc/N2cc functional dissociation was obtained since N2cc, but not N2pc, was modulated by the stimulus position.
3) N2pc is modulated by stimulus-stimulus incongruence (i.e., a conflict of spatial information) but not by stimulus-response incompatibilities. It could be

demonstrated that N2pc was modulated by stimulus-stimulus conflict (S-S) and not by stimulus-response interferences (S-R) because, in the study 2, N2pc was smaller when a conflict of spatial information (S-S conflict) took place, regardless the co-occurrence of motor interferences.

4) Stimulus-response incompatibilities (S-R) interfered at the motor execution stage. It was demonstrated in the Study 3 (where the tasks SRC-p and SRC-d were compared) by means of the lateralized readiness potential (LRP); however, only the stimulus position affected processes that link stimulus evaluation and response selection since the stimulus position, but not the direction pointed by the arrow, modulated the P3b component.
5) In the context of the neuropsychological ageing, evidence for the heterogeneity in the pattern of slowing on each cognitive process was obtained. The above heterogeneity was evidenced because the motor execution stage (whose correlate is the LRP-r onset) was progressively delayed with age; however, the visuospatial processes were similarly delayed in middle-aged and elderly in comparison to young participants but differences were not present between the two older groups. Also, results from the distributional suggested a disproportionate age-related slowing in processing the arrow direction compared to processing the colour and stimulus position.
6) An appropriate biomarker of aMCI was obtained: the amplitude of the LRP-r. Concretely, the area under curve was 0.86. For a cut-off of -3.75 μV, sensitivity and specificity values were 0.85 and 0.92, respectively.
7) Besides obtaining an aMCI biomarker, the allocation of attentional resources for processing the target stimulus (measured by N2pc amplitude) was reduced in aMCI participants whereby LRP-r and also N2pc are ERP correlates of aMCI.

Differences in behavioural performance (reaction time, percentage of errors, interference effect) between healthy adults and aMCI participants were not obtained. However, ERP correlates suggested the existence of declined physiological processes in aMCI. It suggests, in accordance with Markesbery (2010), that pathophysiological processes in Alzheimer`s disease (AD) start years before the onset of symptoms. Importantly, ERP seems to be a good approach to detect a deficit in functioning before the onset of the clinical symptoms, which should be to encourage efforts for describing a pattern of functioning (even at previous stages regarding the onset of the MCI) that allows to differentiate healthy adults from those who might evolve to MCI and subsequently to AD. It would allow very early interventions in the progression to AD.

Conclusiones

En estudios previos no se investigó la modulación de N2cc en tareas Simon mientras que los estudios que se centraron sobre modulaciones de N2pc en este tipo de tareas son escasos y mostraron resultados contradictorios. La razón para la ausencia de estudios sobre N2cc y N2pc es que la mayoría de los trabajos presentaron los estímulos en una disposición vertical porque resultaba más apropiado para estudiar el locus de interferencia del efecto Simon mediante el potencial de preparación lateralizado (PPL). Sin embargo, N2cc y N2pc merecían ser estudiados ya que N2cc parece implicado en impedir respuestas sobre la base del cambio atencional hacia la posición del estímulo, lo cual es clave para emitir la respuesta correcta en una condición de tarea que requiere una respuesta espacialmente incompatible. Además, N2pc fue relacionado con el procesamiento visoespacial de estímulos lateralizados y de hecho en la tarea Simon el estímulo target está lateralizado. Por otra parte, la presente investigación se centró sobre los efectos de la edad y el deterioro cognitivo ligero sobre los correlatos electrofisiológicos de los procesos cognitivos estudiados. Las principales conclusiones de este estudio fueron las siguientes:

1) N2cc es un correlato de control cognitivo en tareas Simon que actúa monitorizando la selección de la respuesta correcta e impidiendo que la dirección de la atención espacial hacia el estímulo predisponga la selección y emisión de una respuesta con la mano ipsilateral con respecto a la dirección del cambio atencional. Esta conclusión se basó sobre la siguiente evidencia: la actividad premotora (relacionada con N2cc) fue mayor, entre 150-200 ms, en las condiciones donde los estímulos estaban espacialmente lateralizados (CD e IP) que en la condición neutral (NP), como reveló el análisis eLORETA. Además, N2cc fue mayor en IP que en CP, como evidenciaron

las ondas L-NP. Esto fue consistente con una mayor necesidad para monitorizar la selección de la respuesta correcta cuando esta es espacialmente contralateral con respecto a la dirección de la atención espacial.

2) Se obtuvo evidencia sobre la disociación funcional entre N2cc y N2pc ya que el efecto Simon (esto es, la incompatibilidad de la posición del estímulo) moduló N2cc pero no N2pc.
3) N2pc es modulado por un conflicto estímulo-estímulo (E-E) pero no por incompatibilidades estímulo-respuesta (E-R), las cuales afectaron a procesos motores. La modulación de N2pc por el conflicto E-E fue evidenciada en el Estudio 2, en el cual la amplitud de N2pc fue menor en aquellas condiciones donde el conflicto E-E estaba presente, con independencia de la coocurrencia de las interferencias E-R.
4) Las incompatibilidades de la posición del estímulo y la dirección de la flecha comparten un locus de interferencia en el estadio de ejecución de la respuesta, lo cual se estudió mediante el potencial de preparación lateralizado en relación con la respuesta (PPL-r) en las tareas CER-p y CER-d. Sin embargo, sólo la incompatibilidad de la posición afectaba a procesos que vinculan la evaluación del estímulo y la selección de la respuesta puesto que P3b fue modulada en la tarea CER-p pero no en la tarea CER-d.
5) La presente investigación obtuvo evidencia sobre la heterogeneidad en el patrón de enlentecimiento para cada proceso cognitivo. Mientras que el estadio de ejecución de la respuesta fue progresivamente enlentecido con la edad, los procesos de atención visoespacial al estímulo target fueron más lentos en los participantes de mediana edad y mayores que en los

participantes jóvenes. Sin embargo, no hubo diferencias significativas entre el grupo de mediana edad y el de mayores. Además, los resultados del análisis de distribución de tiempos de reacción sugirieron un enlentecimiento relacionado con la edad desproporcionadamente mayor para el procesamiento de la dirección de la flecha que para el procesamiento del color y de su posición.

6) Se obtuvo un biomarcador apropiado del deterioro cognitivo ligero amnésico (DCLa): la amplitud del PPL-r. Concretamente, el área bajo la curva fue 0.86. Utilizando un punto de corte de -3.75 μV, se obtuvo una sensibilidad de 0.85 y una especificidad de 0.92.
7) Además de obtener un biomarcador de DCLa, los resultados mostraron que la asignación de recursos atencionales para procesar el estímulo target (cuyo correlato fue la amplitud de N2pc) se redujo en los participantes con DCLa. Por lo tanto, la amplitud de N2pc, así como la amplitud del PPL-r, son correlatos electrofisiológicos del DCLa.

No se encontraron diferencias en el rendimiento conductual (tiempo de reacción, porcentaje de errores, efecto de interferencia) entre adultos sanos y participantes con DCLa. Sin embargo, los PE mostraron la existencia de diferencias fisiológicas entre los dos grupos de participantes. Este resultado sugiere, tal y como concluyó Markesbery (2010), que los procesos fisiopatológicos implicados en la enfermedad de Alzheimer (EA) preceden en varios años al inicio de la sintomatología. En este sentido, es importante resaltar que los PE mostraron ser un enfoque adecuado para detectar déficits electrofisiológicos antes de la aparición de déficits conductuales. Este hecho podría llevar a plantear estudios encaminados a la descripción de un patrón de funcionamiento que permita diferenciar (incluso antes del inicio del DCL) aquellos adultos sanos que

tienen mayor probabilidad de evolucionar a DCL y posteriormente a EA, lo cual permitiría intervenir de forma muy temprana.

5. Future studies

Considering that the different MCI subtypes (i.e. MCI non-amnestic, MCI single-domain amnestic, MCI multi-domain amnestic) were related to differences in symptoms but also to differences in probability of evolving to Alzheimer`s disease (Petersen & Selamawit, 2008), an ongoing study is investigating the possibility of distinguishing specific electrophysiological correlates for each MCI subtype. Also, in addition to obtaining further MCI biomarkers, future investigations will focus on results from a second evaluation in order to study the evolution of the participants and testing the predictive value of the obtained MCI biomarkers. On the other hand, based on the training carried out in the functional magnetic resonance image (fMRI) technique during the two research stays at University of Bremen, a future investigation will focus on the design of an fMRI study for advancing in the knowledge of the common and specific brain mechanisms involved in resolving different types of SRC interferences.

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